SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-073061- -00000-0000

Fecha: 2012-05-04 13:17:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 300

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE CINASAS, E INDICACIONES PARA ELLO

SOLICITANTE: PLEXXIKON, INC.

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 04 de Mayo de 2012

P2012/000057

OLARTEMOURE

OLARTE MOURE & ASOCI

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-073061- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 300

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2012/000057**

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
Lugar de Constitución: Estado Unidos
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
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2010/055519 Fecha Noviembre 04, 2010

Publicación Internacional No. WO 2011/057022 Fecha Mayo 12, 2011

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

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

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Noviembre 06, 2009	61/259,093

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

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso. Adjunto copia simple ver expediente No.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2010/055519

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

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

Ryan BREMER
476 Weldon Avenue, Apt. 3,
Oakland, CA 94610
Estados Unidos de América
Nacionalidad: Estadounidense

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

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

IX

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0037964

Bogotá D.C., Abril 18 de 2012 - 16:09:42

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	455539755	10/04/2012	5.355.000.00

*** Conceptos Pagados ***

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

==========

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

Responsable: _____
-*********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-073061- -00000-0000

Fecha: 2012-05-04 13:17:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 300

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

Nota del Traductor:

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

Manuscrito: "Ver reconocimiento adjunto"

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

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

www.sdarcc.com

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

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

Traductor Oficial
JORGE E. SIERRA REYES

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

Fecha: 1º de Junio de 2006.

Firmado en constancia,

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

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

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

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

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

Sello.

Apostilla adjunta:

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

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

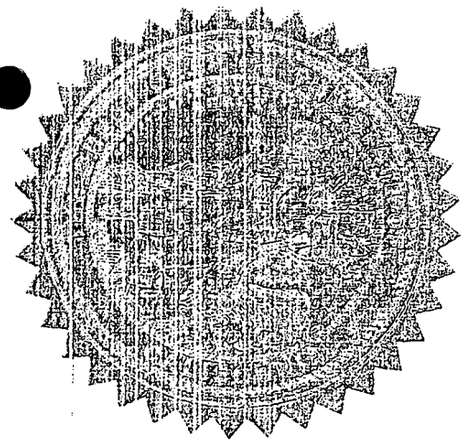
SECRETARY OF STATE
APOSTILLE

(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

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

Branch Offices Available To Serve You

CHULA VISTA
200 Third Avenue
a Vista, CA 91910-5617
(619) 498-2200

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

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

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

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

10

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

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

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

PLEXXIKON, INC.

domiciled in

domiciliado en

91 Bolivar Drive, Suite A, Berkeley, CA 94710 USA

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

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

Signature/Firma:

Date/Fecha: 1/16/06

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

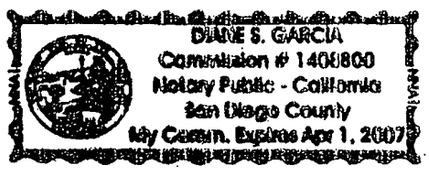
See attached acknowledgment

11

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	**Certificación Notarial**
On this date, January 16, 2006 The undersigned Notary Public certifies:	En esta fecha, el Notario Público suscrito certifica:
1. That Dean R. Artis of legal age and domiciled in 91 Bolivar Drive, Berkeley, California 94710 USA signed the foregoing document.	1. Que mayor de edad y domiciliado suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as Vice President of Plexxikon, Inc.	2. Que el otorgante ha suscrito el referido documento en su carácter de de
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. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.
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.	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



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

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

Fecha: 8 de Mayo de 2006.

Firmado en constancia,

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

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

Oficinas disponibles para servirle:

Chula Vista El Cajon Kearny Mesa San Marcos

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

La suscrita, Kathleen Sereda Glaub, certifica lo siguiente:

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

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1003

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

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

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

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS DE CALIFORNIA

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

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

15

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

16

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by GREGORY J. SMITH*
3. *acting in the capacity of COUNTY ASSESSOR/RECORDER/CLERK*
4. *bears the seal/stamp of the county of SAN DIEGO*
   State of California

CERTIFIED

5. *At SAN DIEGO, California*
6. *The 8TH day of MAY, 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 137384*
9. *Stamp/Seal*
10. *Signature*

Secretary of State

BY

P-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

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16

CERTIFICATE OF THE PRESIDENT AND SECRETARY

OF

PLEXXIKON INC.

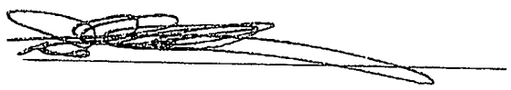
91 Bolivar Drive
Berkeley, CA 94710

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

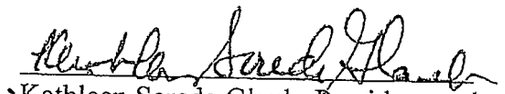
1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

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

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

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

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



Kathleen Sereda Glaub, President and Secretary

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of SAN DIEGO } ss.

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

personally appeared DEAN RICHARD ARMS KATHLEEN SEREDA GLA (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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(71) Applicant *(for all designated States except US)*: **PLEXXIKON, INC.** [US/US]; 91 Bolivar Drive, Suite A, Berkeley, CA 94710 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHANG, Jiazhong** [CN/US]; 888 Foster City Blvd., Apt. Q4, Foster City, CA 94404 (US). **IBRAHIM, Prabha, N.** [US/US]; 3380 Lubich Drive, Mountain View, CA 94040 (US). **BREMER, Ryan** [US/US]; 476 Weldon Avenue, Apt. 3, Oakland, CA 94610 (US). **SPEVAK, Wayne** [US/US]; 1585 Campus Drive, Berkeley, California 94708 (US). **CHO, Hanna** [US/US]; 4363 Terrabella Place, Oakland, California 94619 (US).

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

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

(57) Abstract: Compounds and salts thereof, formulations thereof, conjugates thereof, derivatives thereof, forms thereof and uses thereof are described. In certain aspects and embodiments, the described compounds or salts thereof, formulations thereof, conjugates thereof, derivatives thereof, or forms thereof are active on Fms protein kinase, or on Fms and Kit protein kinase, or on Fms and Flt-3 protein kinase. Also described are methods of use thereof to treat diseases and conditions, including diseases and conditions associated with activity of Fms protein kinase, Kit protein kinase, or Flt-3 protein kinase including rheumatoid arthiritis, osteoarthritis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, renal hypertrophy, acute myeloid leukemia, melanoma, multiple myeloma, metastatic breast cancer, prostate cancer, pancreatic cancer, neurofibromatosis, brain metastases, and gastrointestinal stromal 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 Fms kinase inhibitors. In certain embodiments disclosed compounds are both Fms and Kit kinase inhibitors. In certain embodiments disclosed compounds are both Fms and Flt-3 kinase inhibitors.

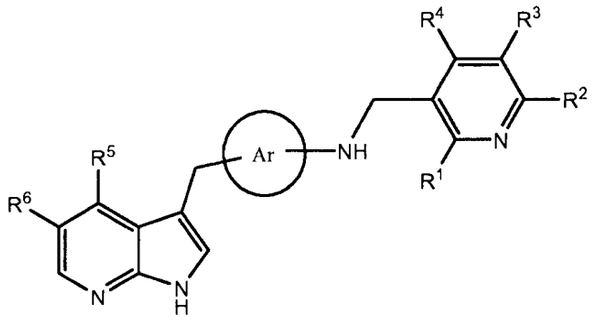
SUMMARY OF THE INVENTION

[0002] In certain aspects and embodiments disclosed herein, compounds are provided, as well as various salts thereof, formulations thereof, conjugates thereof, derivatives thereof, forms thereof and uses thereof. In some embodiments, compounds are of Formula I', Formula I, Formula II', Formula II, Formula IIa, Formula III' or Formula III as described below. In certain embodiments, the compounds inhibit Fms protein kinase selectively relative to other protein kinases, including Kit and Flt-3 protein kinases. In certain embodiments, the compounds inhibit both Fms protein kinase and Kit protein kinase. In certain embodiments, the compounds inhibit both Fms protein kinase and Flt-3 protein kinase. In certain embodiments, the compounds inhibit each of Fms protein kinase, Kit protein kinase and Flt-3 protein kinase.

[0003] Also contemplated in accordance with the present invention are methods for the use of the compounds in treating diseases and conditions associated with regulation of the activity of any of Fms protein kinase, Kit protein kinase, and Flt-3 protein kinase, including any mutations of these kinases. 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 modulation of Fms kinase, Fms and Kit kinases, Fms and Flt-3 kinases, or Fms, Kit and Flt-3 kinases including 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, 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 mycloma, metastatic 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.

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

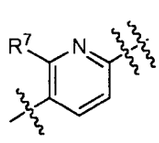


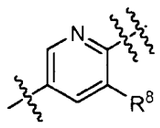
Formula I'

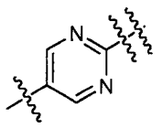
or a salt, a prodrug, a tautomer or a stereoisomer thereof,

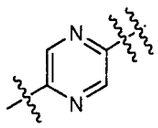
wherein:

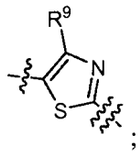
Ar is selected from the group consisting of:



,


,


,


, and


; wherein

indicates the point of attachment of Ar to -CH_2- of Formula I' and wherein

indicates the point of attachment of Ar to -NH- of Formula I';

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of –H, halogen, lower alkyl, halogen substituted lower alkyl, halogen substituted lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{40}, -$S(O)_2$-R^{41}, -$S(O)_2$-N(H)-R^{42}, -N(H)-R^{42}, -$N(R^{42})_2$, and -N(H)-$S(O)_2$-R^{43}, provided that at least two of R^1, R^2, R^3 and R^4 are –H and one of R^1, R^2, R^3 and R^4 is other than hydrogen, wherein:

R^{40} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{41}, R^{42} and R^{43} are lower alkyl;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10}, -C(O)-N(H)-R^{11},

-C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is H, halogen, or lower alkyl;

R^8 is H, halogen, or lower alkoxy;

R^9 is H or halogen;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH_3, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

R^{12} and R^{15} are each independently lower alkyl,

with the proviso that the compound is other than those set forth in Table 1.

[0005] In some embodiments, R^1, R^3 and R^4 are each independently selected from the group consisting of –H, lower alkoxy, halogen, halogen substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{40}, -$S(O)_2$-R^{41}, -$S(O)_2$-N(H)-R^{42}, -N(H)-R^{42}, -N(R^{42})$_2$, and -N(H)-$S(O)_2$-R^{43}, provided that at least two of R^1, R^2, R^3 and R^4 are -H and R^2 is -F, -Cl or -Br; or R^1, R^2 and R^3 are -H and R^4 is -CF_3; or R^1 and R^4 are -H, R^2 is -O-CH_3, and R^3 is -F; or R^2 and R^4 are -H, R^1 is -O-CH_3, and R^3 is -F;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is -H, -F, -Cl, or -CH_3;

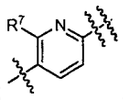
R^8 is -H, -F, -CH_3, or -O-CH_3;

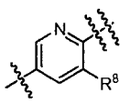
R^9 is -H or -Cl;

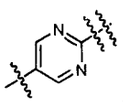
R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH_3, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

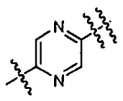
R^{11} and R^{14} are independently hydrogen or lower alkyl; and

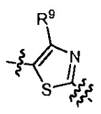
R^{12} and R^{15} are independently lower alkyl.

[0006] In some embodiments, Ar is:  , wherein R^7 is as defined herein.

[0007] In some embodiments, Ar is  , wherein R^8 is as defined herein.

[0008] In some embodiments, Ar is  .

[0009] In some embodiments, Ar is  .

[0010] In some embodiments,  , wherein R^9 is as defined herein.

[0011] In some embodiments, R^1, R^3 and R^4 are H and R^2 is halogen. In other embodiments, R^1, R^2 and R^3 are -H and R^4 is halo substituted lower alkyl. In other embodiments, R^1 and R^4 are –H and R^2 is lower alkoxy. In some embodiements, R^3 is halogen. In yet other embodiments, R^2 and R^4 are -H, R^1 is lower alkoxy and R^3 is halogen. In certain instances, i) R^1, R^2 and R^3 are -H and R^4 is CF_3; or ii) R^1 and R^4 are –H and R^2 is $–OCH_3$; or iii) R^3 is F; or iv) R^2 and R^4 are -H, R^1 is OCH_3 and R^3 is F. The variables R^5, R^6 and Ar are as defined herein.

[0012] In some embodiments of compounds of Formula I', R^5 is -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. In certain instances, R^5 is H. All the other variables are as defined herein.

[0013] In some embodiments of compounds of Formula I', R^5 is -H. In some embodiments, R^5 is -H and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -$NHC(O)CH_3$, -$NHS(O)_2CH_3$, or cyclopropyl. All the other variables are as defined herein.

[0014] In some embodiments of compounds of Formula I', R^6 is selected from the group consisting of H, halo, lower alkyl, lower alkoxy, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15},

$-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, and $-N(H)-S(O)_2-R^{15}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. In certain instances, R^6 is halo, lower alkyl or fluoro substituted lower alkyl. All the other variables are as defined herein.

[0015] In some embodiments of compounds of Formula I', R^6 is -H. In some embodiments, R^6 is -H and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl. In other embodiments, R^6 is halo, lower alkyl lower alkoxy, or fluoro substituted lower alkyl. In yet other embodiments, R^6 is halogen, methyl, methoxy, trifluoromethyl, or CN. All the other variables are as defined herein.

[0016] In some embodiments of compounds of Formula I', R^7 is H, halogen or lower alkyl. In other embodiments, R^7 is H, -F, -Cl, Br or $-CH_3$. All the other variables are as defined herein.

[0017] In some embodiments of compounds of Formula I', R^8 is H, halogen or lower alkoxy. In other embodiments, R^8 is H, -F, -Cl, Br or $-OCH_3$. All the other variables are as defined herein.

[0018] In some embodiments of compounds of Formula I', R^9 is H or halogen. In other embodiments, R^9 is -H or –Cl. All the other variables are as defined herein.

[0019] In some embodiments of compounds of Formula I', R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; and R^5 is -H. In some embodiments, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; R^5 is -H; and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, or cyclopropyl. All the other variables are as defined herein.

[0020] In some embodiments of compounds of Formula I', R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; and R^6 is -H. In some embodiments, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl. All the other variables are as defined herein.

[0021] In some embodiments of compounds of Formula I', R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; and R^5 is -H. In some embodiments, R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; R^5 is -H; and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, or cyclopropyl. All the other variables are as defined herein.

[0022] In some embodiments of compounds of Formula I', R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; and R^6 is -H. In some embodiments, R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl. All the other variables are as defined herein.

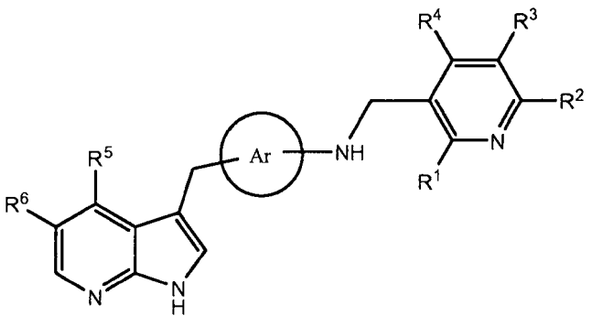
[0023] In some embodiments of compounds of Formula I', R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is -F; and R^5 is -H. In some embodiments, R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is-F; R^5 is -H; and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, or cyclopropyl. All the other variables are as defined herein.

[0024] In some embodiments of compounds of Formula I', R^1 and R^4 are -H; R^2 is -O-CH_3; R^3 is -F; and R^6 is -H. In some embodiments, R^1 and R^4 are -H; R^2 is -O-CH_3; R^3 is -F; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, -O-CH_3, or phenyl. All the other variables are as defined herein.

[0025] In some embodiments of compounds of Formula I', R^2 and R^4 are -H; R^1 is -O-CH_3; R^3 is -F; and R^5 is -H. In some embodiments, R^2 and R^4 are -H; R^1 is -O-CH_3; R^3 is -F; R^5 is -H; and R^6 is -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -S(O)$_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -NHS(O)$_2CH_3$, or cyclopropyl. All the other variables are as defined herein.

[0026] In some embodiments of compounds of Formula I', R^2 and R^4 are -H; R^1 is -O-CH_3; R^3 is -F; and R^6 is -H. In some embodiments, R^2 and R^4 are -H; R^1 is -O-CH_3; R^3 is -F; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, -O-CH_3, or phenyl. All the other variables are as defined herein.

[0027] In another aspect, compounds having the structure according to the following Formula I are provided:

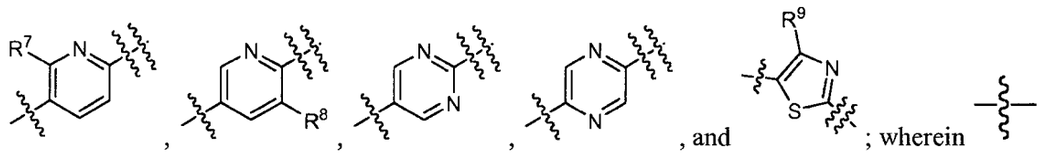


Formula I

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

wherein:

Ar is selected from the group consisting of:



; wherein indicates the point of attachment of Ar to -CH_2- of Formula I and wherein  indicates the point of attachment of Ar to -NH- of Formula I;

R^1, R^3 and R^4 are -H and R^2 is -F, -Cl or -Br; or R^1, R^2 and R^3 are -H and R^4 is -CF_3; or R^1 and R^4 are -H, R^2 is -O-CH_3, and R^3 is -F; or R^2 and R^4 are -H, R^1 is -O-CH_3, and R^3 is -F;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10},

-C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is -H, -F, -Cl, or -CH_3;

R^8 is -H, -F, -CH_3, or -O-CH_3;

R^9 is -H or -Cl;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH_3, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

R^{12} and R^{15} are independently lower alkyl.

[0028] In some embodiments of compounds of Formula I, R^5 is -H. In some embodiments, R^5 is -H and R^6 is -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -NHS$(O)_2CH_3$, or cyclopropyl.

[0029] In some embodiments of compounds of Formula I, R^6 is -H. In some embodiments, R^6 is -H and R^5 is -H, -Cl, -CN, -C≡CH, -O-CH_3, or phenyl.

[0030] In some embodiments of compounds of Formula I, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; and R^5 is -H. In some embodiments, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; R^5 is -H; and R^6 is -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -NHS$(O)_2CH_3$, or cyclopropyl.

[0031] In some embodiments of compounds of Formula I, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; and R^6 is -H. In some embodiments, R^1, R^3 and R^4 are -H; R^2 is -F, -Cl or -Br; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, -O-CH_3, or phenyl.

[0032] In some embodiments of compounds of Formula I, R^1, R^2 and R^3 are -H; and R^4 is -CF_3; and R^5 is -H. In some embodiments, R^1, R^2 and R^3 are -H; and R^4 is -CF_3; R^5 is -H; and R^6 is -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -NHS$(O)_2CH_3$, or cyclopropyl.

[0033] In some embodiments of compounds of Formula I, R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; and R^6 is -H. In some embodiments, R^1, R^2 and R^3 are -H; and R^4 is $-CF_3$; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl.

[0034] In some embodiments of compounds of Formula I, R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is -F; and R^5 is -H. In some embodiments, R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is-F; R^5 is -H; and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, or cyclopropyl.

[0035] In some embodiments of compounds of Formula I, R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is -F; and R^6 is -H. In some embodiments, R^1 and R^4 are -H; R^2 is $-O-CH_3$; R^3 is -F; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl.

[0036] In some embodiments of compounds of Formula I, R^2 and R^4 are -H; R^1 is $-O-CH_3$; R^3 is -F; and R^5 is -H. In some embodiments, R^2 and R^4 are -H; R^1 is $-O-CH_3$; R^3 is -F; R^5 is -H; and R^6 is -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, or cyclopropyl.

[0037] In some embodiments of compounds of Formula I, R^2 and R^4 are -H; R^1 is $-O-CH_3$; R^3 is -F; and R^6 is -H. In some embodiments, R^2 and R^4 are -H; R^1 is $-O-CH_3$; R^3 is -F; R^6 is -H; and R^5 is -H, -Cl, -CN, -C≡CH, $-O-CH_3$, or phenyl.

[0038] In one embodiment of compounds of Formulae I and I', the compound is selected from the group consisting of:
[5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1497**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1498**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1499**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1500**),
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1501**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1502**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1403**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1504**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1505**),

[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1506**),

(6-Chloro-pyridin-3-ylmethyl)-[6-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1508**),

[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1509**),

[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1510**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1513**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1515**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1516**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1520**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1521**),

(6-Chloro-pyridin-3-ylmethyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1523**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1524**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1525**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1528**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1529**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1531**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1533**),

(6-Chloro-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-

2-yl]-amine (**P-1535**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1536**),
[6-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1537**),
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1540**),
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-chloro-pyridin-3-ylmethyl)-amine (**P-1542**),
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1543**),
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1544**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1547**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1548**),
(6-Chloro-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1550**),
[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1551**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1555**),
(6-Chloro-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1557**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1558**),
[3-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1559**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1563**),
(6-Chloro-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1565**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1566**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1567**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1570**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1579**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1581**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1582**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1584**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1586**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1587**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1588**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1590**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-chloro-pyridin-3-ylmethyl)-amine (**P-1592**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1593**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1594**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1597**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1598**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1599**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1600**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1602**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1603**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-

yl]-amine (**P-1607**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1608**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1611**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1612**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1613**),
[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1623**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1625**),
[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1626**),
[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1627**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1630**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1632**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1633**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1634**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1638**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1640**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1641**),
(4-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1642**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1646**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1648**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1649**),

[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1650**),

3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1654**),

3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1655**),

3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1656**),

3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1657**),

[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1661**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1663**),

[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1664**),

[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1665**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1670**),

N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1672**),

N-(3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1673**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1677**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1680**),

N-(3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1681**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1685**),

(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1687**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-

methoxy-pyridin-3-ylmethyl)-amine (**P-1688**),
[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1689**),
3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**P-1693**),
3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1694**),
3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1696**),
3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1697**),
3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1698**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1703**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1704**),
(6-Chloro-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1706**),
{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1707**),
[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1711**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1713**),
[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1714**),
[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1715**),
3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1720**),
3-{6-[(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1721**),
3-{6-[(4-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1722**),
3-{6-[(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1726**),

(6-Bromo-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2002**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine (**P-2004**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2040**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2041**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2042**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2062**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2063**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2064**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2070**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2073**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2078**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2088**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2152**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2153**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-

pyridin-3-ylmethyl)-amine (**P-2165**),
[5-(4-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2170**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(4-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2171**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**, and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0039] In some embodiments of compounds of Formulae I and I', R^7 is other than hydrogen. All the other variables are as defined herein.

[0040] In one group of embodiments of compounds of Formulae I and I', R^6 and R^7 are not simulataneously H. All the other variables are as defined herein.

[0041] In another group of embodiments of compounds of Formulae I and I', when R^7 is halogen, R^6 is other than H, halogen, heteroaryl, CN or lower alkyl. In certain instances, when R^7 is Cl, R^6 is other than H, Cl, pyrrazolyl, CN or CH_3. All the other variables are as defined herein.

[0042] In another group of embodiments of compounds of Formulae I and I', when R^7 is halogen, R^6 is other than halo substituted lower alkyl. In certain instances, when R^7 is Cl, R^6 is other than CF_3. All the other variables are as defined herein.

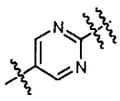
[0043] In one group of embodiments of compounds of Formulae I and I', when R^7 is halogen, R^2 is other than halogen substituted lower alkyl or lower alkoxy. In certain instances, when R^7 is F, R^2 is other than CF_3 or $-OCH_3$. All the other variables are as defined herein.

[0044] In another group of embodiments of compounds of Formulae I and I', when R^7 is halogen, R^6 is other than halogen, lower alkoxy, hydrogen or CN. In certain instances, when R^7 is -F, R^6 is other than Cl, OCH_3, hydrogen or CN. In other instances, when R^7 is -F, R^3 is other than F. All the other variables are as defined herein.

[0045] In one group of embodiments of compounds of Formulae I and I', when R^7 is hydrogen, R^6 is other than halogen, hydrogen, lower alkyl, CN, or lower alkoxy. In certain instances, when R^7 is hydrogen, R^6 is other than H, Cl, F, CH_3, CN, $-OCH_3$. All the other variables are as defined herein.

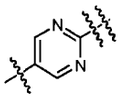
[0046] In another group of embodiments of compounds of Formulae I and I', when R^9 is halogen, R^6 is other than H or halogen. In certain instances, when R^9 is Cl, R^6 is other than H or Cl. All the other variables are as defined herein.

[0047] In another group of embodiments of compounds of Formulae I and I', when Ar is



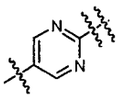
, R^6 is other than hydrogen. All the other variables are as defined herein.

[0048] In another group of embodiments of compounds of Formulae I and I', when Ar is



, R^1, R^2, R^3 and R^4 are not simultaneously hydrogen. All the other variables are as defined herein.

[0049] In another group of embodiments of compounds of Formulae I and I', when Ar is



, R^2 is other than halo substuted lower alkyl, for example, in one embodiment, R^2 is other than CF_3. All the other variables are as defined herein.

[0050] The compounds excluded from Formula I' and Formula I are listed in Table 1 below.

Table 1

[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0174)**,

[6-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0176)**,

{6-Chloro-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0179)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0186)**,

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0187)**,

[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0188)**,

3-{2-Chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0232)**,

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0233)**,

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0234)**,

[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0378)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0379)**,

(5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0414)**,

3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0415)**,

3-[6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0432)**,

Pyridin-3-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0094)**,

(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0215)**,

(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0219)**,

(5-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0222)**;

(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0230)**,

3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0273)**,

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0282)**,

3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0284)**,

(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0285)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine **(P-0286)**,

3-{6-[(2-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0287)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **(P-0324)**,

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0331)**,

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0332)**,

(2-Morpholin-4-yl-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0347)**,

(2,6-Dimethoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0370)**,

(6-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0374)**,

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine **(P-0376)**,

(5-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0400)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine **(P-0409)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0181**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0182**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine **(P-0164)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0173)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-0422**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0429**),

2,2-Dimethyl-N-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-propionamide **(P-0384)**,

Methyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine **(P-0385)**,

Dimethyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine **(P-0399)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine (**P-0200**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**P-0236**),

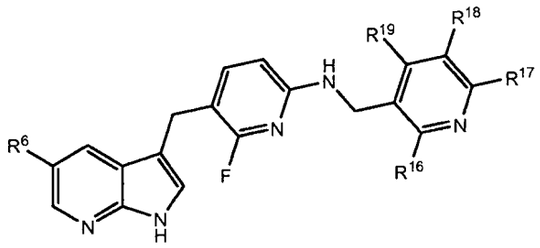
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-0241**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0242**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-0247**), and

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-0207**).

[0051] In a second aspect, the present invention provides compounds having Formula II':



Formula II'

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

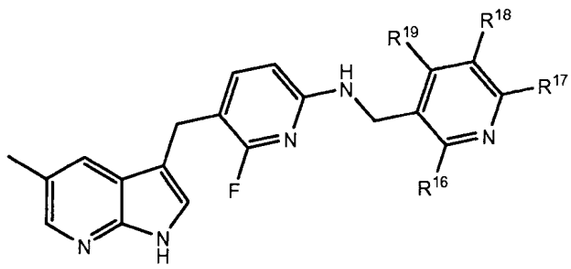
wherein:

R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from the group consisting of H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-$S(O)_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H;

R^{20} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl; R^{21} is lower alkyl; R^{22} is lower alkyl; and R^{23} is lower alkyl.

[0052] In some embodiments of compounds of Formula II', R^6 is selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. In certain instances, R^6 is F, Cl, Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}. -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} or -N(H)-$S(O)_2$-R^{15}. In other instances, R^6 is methyl, ethyl, propyl, butyl, pentyl or hexyl. All other variables are as defined herein.

[0053] In some embodiments, compounds having the structure according to the following Formula II are provided:



Formula II

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

wherein:

R^{16}, R^{17}, R^{18} and R^{19} are independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, and -N(H)-$S(O)_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H;

R^{20} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{21} is lower alkyl;

R^{22} is lower alkyl; and

R^{23} is lower alkyl.

[0054] In some embodiments of compounds of Formulae II and II', R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, and -N(H)-$S(O)_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are –H. In some embodiments, R^{17} and R^{19} are H, halogen or lower alkyl. All other variables are as defined herein.

[0055] In other embodiments of compounds of Formulae II and II', R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H. All other variables are as defined herein.

[0056] In some embodiments of compounds of Formulae II and II', R^{16}, R^{17}, and R^{18} are H and R^{19} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{17}, and R^{18} are H and R^{19} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{17}, and R^{18} are H and

R^{19} is fluoro substituted lower alkyl or -O-R^{20}. In some embodiments R^{16}, R^{17}, and R^{18} are H and R^{19} is -CF_3 or -O-CH_3. All other variables are as defined herein.

[0057] In some embodiments of compounds of Formulae II and II', R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, or -O-R^{20}. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, or -O-CH_3. All other variables are as defined herein.

[0058] In some embodiments of compounds of Formulae II and II', R^{16}, R^{18}, and R^{19} are H and R^{17} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -Cl, fluoro substituted lower alkyl, cycloalkylamino, or -O-R^{20}. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -Cl, -CF_3, -O-CH_3, or morpholin-4-yl. All other variables are as defined herein.

[0059] In some embodiments of compounds of Formulae II and II', R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -CF_3, morpholin-4-yl, -O-CH_3, -O-CH_2CH_3, -O-$CH(CH_3)_2$, -O-CH_2CF_3, -O-cyclopentyl, -O-cyclohexyl, or -N(H)-CH_3. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -CF_3, or -O-CH_3. All other variables are as defined herein.

[0060] In some embodiments of compounds of Formulae II and II', R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, or -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. All other variables are as defined herein.

[0061] In some embodiments of compounds of Formulae II and II', R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, lower alkyl; fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -CF_3 or -O-CH_3. All other variables are as defined herein.

[0062] In some embodiments of compounds of Formulae II and II', R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F or -O-CH_3. All other variables are as defined herein.

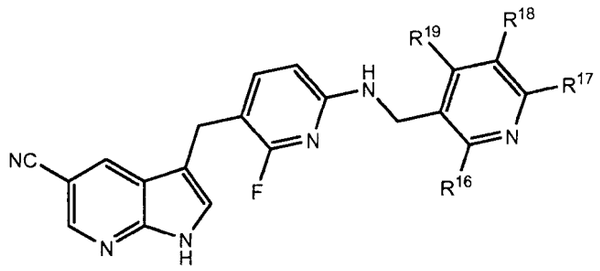
[0063] In some embodiments of compounds of Formulae II and II', R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, lower alkyl; fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. All other variables are as defined herein.

[0064] In some embodiments of compounds of Formula II, R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, or -O-CH_3. All other variables are as defined herein.

[0065] In some embodiments of compounds of Formulae II and II', R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In

some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -CF_3, -O-CH_3, or -N(CH_3)$_2$. All other variables are as defined herein.

[0066] In some embodiments, compounds having the structure according to the following Formula IIa are provided:



Formula IIa

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

wherein:

R^{16}, R^{17}, R^{18} and R^{19} are independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-S(O)$_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H;

R^{20} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{21} is lower alkyl;

R^{22} is lower alkyl; and

R^{23} is lower alkyl.

[0067] In some embodiments of compounds of Formula IIa, R^{16}, R^{17}, R^{18} and R^{19} are each independently from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-S(O)$_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are –H. In some embodiments, R^{17} and R^{19} are H, halogen or lower alkyl. All other variables are as defined herein.

[0068] In other embodiments of compounds of Formula IIa, R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H. All other variables are as defined herein.

[0069] In some embodiments of compounds of Formula IIa, R^{16}, R^{17}, and R^{18} are H and R^{19} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{17}, and R^{18} are H and R^{19} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{17}, and R^{18} are H and R^{19} is fluoro substituted lower alkyl or -O-R^{20}. In some embodiments R^{16}, R^{17}, and R^{18} are H and R^{19} is $-CF_3$ or $-O-CH_3$. All other variables are as defined herein.

[0070] In some embodiments of compounds of Formula IIa, R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, or -O-R^{20}. In some embodiments R^{16}, R^{17}, and R^{19} are H and R^{18} is -F, -Cl, or $-O-CH_3$. All other variables are as defined herein.

[0071] In some embodiments of compounds of Formula IIa, R^{16}, R^{18}, and R^{19} are H and R^{17} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -Cl, fluoro substituted lower alkyl, cycloalkylamino, or -O-R^{20}. In some embodiments R^{16}, R^{18}, and R^{19} are H and R^{17} is -Cl, $-CF_3$, $-O-CH_3$, or morpholin-4-yl. All other variables are as defined herein.

[0072] In some embodiments of compounds of Formula IIa, R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, $-CF_3$, morpholin-4-yl, $-O-CH_3$, $-O-CH_2CH_3$, $-O-CH(CH_3)_2$, $-O-CH_2CF_3$, -O-cyclopentyl, -O-cyclohexyl, or $-N(H)-CH_3$. In some embodiments R^{17}, R^{18}, and R^{19} are H and R^{16} is -F, $-CF_3$, or $-O-CH_3$. All other variables are as defined herein.

[0073] In some embodiments of compounds of Formula IIa, R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, lower alkyl, fluoro

substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{16} and R^{17} are H; and R^{18} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. All other variables are as defined herein.

[0074] In some embodiments of compounds of Formula IIa, R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, or -N(H)-S(O)$_2$-R^{23}. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{16} and R^{18} are H; and R^{17} and R^{19} are independently -CF_3 or -O-CH_3. All other variables are as defined herein.

[0075] In some embodiments of compounds of Formula IIa, R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, or -N(H)-S(O)$_2$-R^{23}. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{16} and R^{19} are H; and R^{17} and R^{18} are independently -F or -O-CH_3. All other variables are as defined herein.

[0076] In some embodiments of compounds of Formula IIa, R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, or -N(H)-S(O)$_2$-R^{23}. In some embodiments R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{17} and R^{18} are H; and R^{16} and R^{19} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. All the other variables are as defined herein.

[0077] In some embodiments of compounds of Formula IIa, R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, or -N(H)-S(O)$_2$-R^{23}. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -N(R^{22})$_2$. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{17} and R^{19} are H; and R^{16} and R^{18} are independently -F, -Cl, or -O-CH_3. All the other variables are as defined herein.

[0078] In some embodiments of compounds of Formula IIa, R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, or -N(H)-$S(O)_2$-R^{23}. In some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{20}, -N(H)-R^{22}, or -$N(R^{22})_2$. In some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -F, -Cl, CF_3, -O-CH_3, or -$N(CH_3)_2$. In some embodiments R^{18} and R^{19} are H; and R^{16} and R^{17} are independently -CF_3, -O-CH_3, or -$N(CH_3)_2$. All the other variables are as defined herein.

[0079] In one embodiment of compounds of Formulae II and II' and IIa, 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]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2027**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),

(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2047**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),

(4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2050**),

(2-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2051**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2052**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-2058**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2062**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-4-ylmethyl)-amine (**P-2065**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2067**),

(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2071**),
(2,5-Dimethoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2086**),
(3,5-Dimethoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2087**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2088**),
(3-Bromo-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2089**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-morpholin-4-yl-pyridin-3-ylmethyl)-amine (**P-2090**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-morpholin-4-yl-pyridin-3-ylmethyl)-amine (**P-2091**),
(3-Chloro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2092**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-2093**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine (**P-2094**),
(5-{[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-methyl-amine (**P-2095**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-2096**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2097**),
(5-Fluoro-2-methanesulfonyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2098**),
(5-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2099**),
(5-Bromo-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2100**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-methyl-pyridin-4-ylmethyl)-amine (**P-2101**),
(3-Chloro-5-fluoro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2102**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-3-ylmethyl)-amine (**P-2103**),

(3,5-Dimethyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2104**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-2105**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyrimidin-5-ylmethyl)-amine (**P-2106**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methylamino-pyridin-3-ylmethyl)-amine (**P-2107**),

(3,5-Bis-trifluoromethyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2108**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-methoxy-pyridin-3-ylmethyl)-amine (**P-2109**),

(2-Ethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2110**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-isopropoxy-pyridin-3-ylmethyl)-amine (**P-2111**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-methyl-pyridin-2-ylmethyl)-amine (**P-2112**),

(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2113**),

(2-Cyclohexyloxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2114**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2115**),

(2-Chloro-5-fluoro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2116**),

4-{[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridine-2-carbonitrile (**P-2117**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-4-ylmethyl)-amine (**P-2118**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-pyridin-4-ylmethyl)-amine (**P-2119**),

(2-Chloro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2120**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-morpholin-4-yl-pyridin-4-ylmethyl)-amine (**P-2121**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-pyrrolidin-1-yl-pyridin-4-ylmethyl)-amine (**P-2122**),
(5-Chloro-2-fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2123**),
(4-Chloro-2-methanesulfonyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2124**),
(2-Dimethylamino-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2125**),
(2-Ethyl-pyrimidin-5-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2126**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-propyl-pyrimidin-5-ylmethyl)-amine (**P-2127**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-isopropyl-pyrimidin-5-ylmethyl)-amine (**P-2128**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2-methoxy-ethyl)-pyrimidin-5-ylmethyl]-amine (**P-2129**),
(2-Butyl-pyrimidin-5-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2130**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methyl-pyridin-2-ylmethyl)-amine (**P-2131**),
(3-Fluoro-5-methyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2132**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-methoxy-5-trifluoromethyl-benzyl)-amine (**P-2133**),
(3-Fluoro-5-methoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2134**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3,4,5-trimethoxy-benzyl)-amine (**P-2150**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2151**),
5-Fluoro-3-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-1-methyl-1H-pyridin-2-one (**P-2156**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2166**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-dimethylamino-6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2167**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2186**),

Ethanesulfonic acid (2-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2198**),

Ethanesulfonic acid (4-fluoro-3-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2199**),

Ethanesulfonic acid (3-fluoro-5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2202**),

5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**

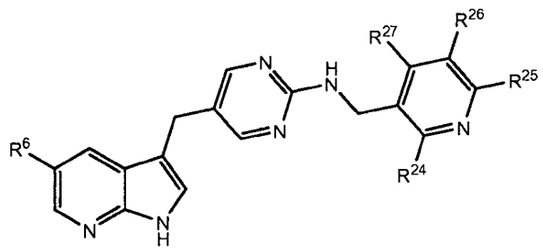
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**

6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**

6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**, and

any salt, prodrug, tautomer, or stereoisomer thereof.

[0080] In a third aspect, the invention provides compounds having Formula III':



Formula III'

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

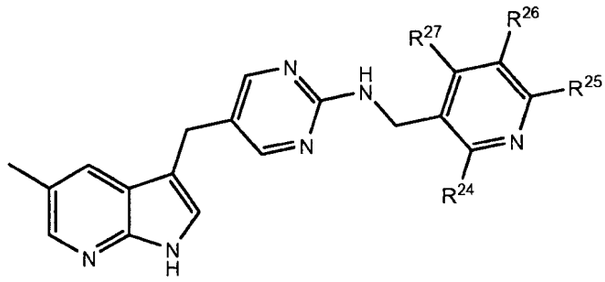
wherein:

R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from the group consisting of -H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -$S(O)_2$-N(H)-R^{30}, -N(H)-R^{30}, -$N(R^{30})_2$, and -N(H)-$S(O)_2$-R^{31}, provided that at least two of R^{24}, R^{25}, R^{26} and R^{27} are -H; R^{28} is lower alkyl,

fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl; R^{29} is lower alkyl;R^{30} is lower alkyl; and R^{31} is lower alkyl.

[0081] In some embodiments of compounds of Formula III', R^6 is selected from the group consisting of halogen, lower alkyl, lower alkoxy, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. In other embodiments of compounds of Formula III', R^6 is F, Cl, Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}. -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} or -N(H)-$S(O)_2$-R^{15}. In some embodiments, R^6 is methyl, ethyl, propyl, butyl, pentyl or hexyl. All other variables are as defined herein.

[0082] In some embodiments, compounds having the structure according to the following Formula III are provided:



Formula III

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

wherein:

R^{24}, R^{25}, R^{26} and R^{27} are independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -$S(O)_2$-N(H)-R^{30}, -N(H)-R^{30}, -N(R^{30})$_2$, and -N(H)-$S(O)_2$-R^{31}, provided that at least two of R^{24}, R^{25}, R^{26} and R^{27} are -H;

R^{28} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{29} is lower alkyl;

R^{30} is lower alkyl; and

R^{31} is lower alkyl.

[0083] In some embodiments of compounds of Formulae III and III', R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-$S(O)_2$-R^{23}, provided that at least two of

R^{24}, R^{25}, R^{26} and R^{27} are –H. In some embodiments, R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl. All other variables are as defined herein.

[0084] In some embodiments of compounds of Formulae III and III', R^{24}, R^{25}, and R^{26} are H and R^{27} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, or -N(H)-$S(O)_2$-R^{31}. In some embodiments R^{24}, R^{25}, and R^{26} are H and R^{27} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -$N(R^{30})_2$. In some embodiments R^{24}, R^{25}, and R^{26} are H and R^{27} is fluoro substituted lower alkyl or -O-R^{28}. In some embodiments R^{24}, R^{25}, and R^{26} are H and R^{27} is $-CF_3$ or $-O-CH_3$. All other variables are as defined herein.

[0085] In some embodiments of compounds of Formulae III and III', R^{24}, R^{25}, and R^{27} are H and R^{26} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, or -N(H)-$S(O)_2$-R^{31}. In some embodiments R^{24}, R^{25}, and R^{27} are H and R^{26} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -$N(R^{30})_2$. In some embodiments R^{24}, R^{25}, and R^{27} are H and R^{26} is -F, -Cl, or -O-R^{28}. In some embodiments R^{24}, R^{25}, and R^{27} are H and R^{26} is -F, -Cl, or $-O-CH_3$. All other variables are as defined herein.

[0086] In some embodiments of compounds of Formulae III and III', R^{24}, R^{26}, and R^{27} are H and R^{25} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, or -N(H)-$S(O)_2$-R^{31}. In some embodiments R^{24}, R^{26}, and R^{27} are H and R^{25} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -$N(R^{30})_2$. In some embodiments R^{24}, R^{26}, and R^{27} are H and R^{25} is -Cl, fluoro substituted lower alkyl, cycloalkylamino, or -O-R^{28}. In some embodiments R^{24}, R^{26}, and R^{27} are H and R^{25} is -Cl, $-CF_3$, $-O-CH_3$, or 4-methyl-piperazin-1-yl. All other variables are as defined herein.

[0087] In some embodiments of compounds of Formulae III and III', R^{25}, R^{26}, and R^{27} are H and R^{24} is -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, or -N(H)-$S(O)_2$-R^{31}. In some embodiments R^{25}, R^{26}, and R^{27} are H and R^{24} is -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -$N(R^{30})_2$. In some embodiments R^{25}, R^{26}, and R^{27} are H and R^{24} is -F, $-CF_3$, morpholin-4-yl, $-O-CH_3$, $-O-CH_2CH_3$, $-O-CH(CH_3)_2$, $-O-CH_2CF_3$, -O-cyclopentyl, -O-cyclohexyl, or $-N(H)-CH_3$. In some embodiments R^{25}, R^{26}, and R^{27} are H and R^{24} is -F, $-CF_3$, $-O-CH_3$, $-O-CH_2CH_3$, or -O-cyclopentyl. All other variables are as defined herein.

[0088] In some embodiments of compounds of Formulae III and III', R^{24} and R^{25} are H; and R^{26} and R^{27} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{24} and R^{25} are H; and R^{26} and R^{27} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{24} and R^{25} are H; and R^{26} and R^{27} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. All other variables are as defined herein.

[0089] In some embodiments of compounds of Formulae III and III', R^{24} and R^{26} are H; and R^{25} and R^{27} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{24} and R^{26} are H; and R^{25} and R^{27} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{24} and R^{26} are H; and R^{25} and R^{27} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{24} and R^{26} are H; and R^{25} and R^{27} are independently -CF_3 or -O-CH_3. All other variables are as defined herein.

[0090] In some embodiments of compounds of Formulae III and III', R^{24} and R^{27} are H; and R^{25} and R^{26} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{24} and R^{27} are H; and R^{25} and R^{26} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{24} and R^{27} are H; and R^{25} and R^{26} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{24} and R^{27} are H; and R^{25} and R^{26} are independently -F or -O-CH_3. All other variables are as defined herein.

[0091] In some embodiments of compounds of Formulae III and III', R^{25} and R^{26} are H; and R^{24} and R^{27} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{25} and R^{26} are H; and R^{24} and R^{27} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{25} and R^{26} are H; and R^{24} and R^{27} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. All other variables are as defined herein.

[0092] In some embodiments of compounds of Formulae III and III', R^{25} and R^{27} are H; and R^{24} and R^{26} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{25} and R^{27} are H; and R^{24} and R^{26} are independently -F, -Cl, lower alkyl, fluoro

substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{25} and R^{27} are H; and R^{24} and R^{26} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{25} and R^{27} are H; and R^{24} and R^{26} are independently -F or -O-CH_3. All other variables are as defined herein.

[0093] In some embodiments of compounds of Formulae III and III', R^{26} and R^{27} are H; and R^{24} and R^{25} are independently -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, or -N(H)-S(O)$_2$-R^{31}. In some embodiments R^{26} and R^{27} are H; and R^{24} and R^{25} are independently -F, -Cl, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, -O-R^{28}, -N(H)-R^{30}, or -N(R^{30})$_2$. In some embodiments R^{26} and R^{27} are H; and R^{24} and R^{25} are independently -F, -Cl, CF_3, -O-CH_3, or -N(CH_3)$_2$. In some embodiments R^{26} and R^{27} are H; and R^{24} and R^{25} are independently -CF_3, -O-CH_3, or -N(CH_3)$_2$. All other variables are as defined herein.

[0094] In one embodiment of compounds of Formulae III and III', the compound is selected from the group consisting of:

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1569**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1570**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2057**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),

(2-Methoxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2069**),

(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2072**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2073**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-2076**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-2077**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2078**),

(6-Methyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

amine (**P-2079**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2080**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-2081**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2082**),
(5-Ethyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2083**),
(3-Methyl-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2084**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-pyridin-4-ylmethyl)-amine (**P-2085**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine (**P-2138**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2139**),
[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylmethyl]-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2140**),
(2-Methyl-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2141**),
(2-Ethoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2142**),
(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2148**),
(2-Cyclopentyloxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2149**), and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0095] In a fourth aspect, compounds are provided, wherein the compound is selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**P-1496**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1507**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1511**),

[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1512**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1514**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1517**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1518**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1519**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1522**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1526**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1527**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1530**),

(6-Methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1532**),

(5-Fluoro-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1534**),

[6-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1538**),

(2-Methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1539**),

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1541**),

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1545**),

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1546**),

(5-Fluoro-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1549**),

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1552**),

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-

ylmethyl)-amine (**P-1553**),
(6-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1554**),
(5-Fluoro-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1556**),
[3-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1560**),
(2-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1561**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1562**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1564**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1568**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1580**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1583**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1585**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1589**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1591**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1595**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1596**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1601**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1604**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1605**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1606**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1609**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1614**),

[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1622**),

[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1624**),

[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1628**),

[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1629**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1631**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1635**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1636**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1637**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1639**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1643**),

(6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1644**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1645**),

(5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1647**),

[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1651**),

[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1652**),

[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1653**),

3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-

b]pyridine-5-carbonitrile (**P-1658**),
3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1659**),
3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1660**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1662**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1666**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1667**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1668**),
N-(3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1671**),
N-(3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1674**),
N-(3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1675**),
N-(3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1676**),
N-(3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1678**),
N-(3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1682**),
N-(3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1683**),
N-(3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1684**),
[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1686**),
[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1690**),
[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1691**),
[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1692**),

3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1695**),

3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1699**),

3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1700**),

3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1701**),

4-[4-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**P-1702**),

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1705**),

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1708**),

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1709**),

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1710**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1712**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1716**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1717**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1718**),

3-{6-[(5-Fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1719**),

3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1723**),

3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1724**),

3-{6-[(2-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1725**),

[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1727**),

(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-

pyridin-2-yl]-amine (**P-1728**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-1729**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1730**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1731**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1732**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-1733**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1734**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2001**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-2005**),
(3-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine (**P-2006**),
(3-Chloro-4-methyl-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2007**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,4-difluoro-benzyl)-amine (**P-2008**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl)-amine (**P-2009**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethoxy-benzyl)-amine (**P-2010**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-amine (**P-2011**),
(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-2012**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-methyl-benzyl)-amine (**P-2013**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-4-methyl-benzyl)-amine (**P-2014**),
[2-(3-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2015**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-2016**),

[5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2017**),

[5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2018**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),

[2-(2-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2020**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[2-(4-fluoro-phenyl)-ethyl]-amine (**P-2021**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[2-(6-methyl-pyridin-2-yl)-ethyl]-amine (**P-2022**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2023**),

[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2024**),

Butyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2026**),

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2028**),

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2030**),

(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),

(2-Fluoro-benzyl)-[5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2033**),

(2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2034**),

(2-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2035**),

(2-Chloro-benzyl)-[5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2036**),

(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(1-thiazol-2-yl-ethyl)-amine (**P-2039**),

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2043**),

(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2044**),

[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2045**),

[1-(4-Fluoro-phenyl)-propyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2053**),

[1-(4-Fluoro-phenyl)-cyclopropyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2055**),

[(S)-1-(4-Fluoro-phenyl)-ethyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2056**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-4-ylmethyl)-amine (**P-2074**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2075**),

(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2135**),

(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2136**),

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2143**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2144**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2145**),

[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2146**),

[3-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2147**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2154**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2155**),

3-{[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-methyl}-5-fluoro-1-

methyl-1H-pyridin-2-one (**P-2157**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2158**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2159**),
(6-Methoxy-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2162**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine (**P-2163**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**P-2164**),
5-Fluoro-N-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-2-methoxy-nicotinamide (**P-2168**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2172**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2176**),
N-[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-C-phenyl-methanesulfonamide (**P-2181**), and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0096] 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 as described herein (i.e. compounds of the invention), it is understood (unless indicated otherwise) that a compound as described herein includes compounds of Formulae I and I'including all sub-embodiments thereof, compounds of Formulae II, II' and IIa, including all sub-embodiments thereof, compounds of Formulae III and III' including all sub-embodiments thereof, and compounds as listed in the fourth aspect above.

[0097] In a fifth aspect, methods are provided for treating any of a Fms and/or Kit and/or Flt-3 protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. In certain embodiments, the method involves administering to the subject an

effective amount of a compound as described herein in combination with one or more other therapies for the disease or condition.

[0098] In a sixth aspect, the invention provides methods for treating a Fms protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. In one embodiment, the method involves administering to the subject an effective amount of a compound as described herein in combination with one or more other therapies for the disease or condition.

[0099] In a seventh aspect, the invention provides methods for treating a Kit protein kinase mediated disease or condition in an animal subject in need thereof, wherein the method involves administering to the subject an effective amount of any one or more compound(s) as described herein. In one embodiment, the method involves administering to the subject an effective amount of a compound described herein in combination with one or more other therapies for the disease or condition.

[0100] In an eighth aspect, a compound as described herein will have an IC_{50} of less than 500 nm, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM 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.

[0101] In a ninth aspect, a compound as described herein will have an IC_{50} of less than 500 nm, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Kit 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 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.

[0102] In a tenth aspect, a compound as described herein 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 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 CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR. In one embodiment, the dual Fms/Kit inhibitor is a compound selected from the group consisting of:

(6-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1554**),

[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1562**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2003**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine (**P-2004**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,4-difluoro-benzyl)-amine (**P-2008**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-methyl-benzyl)-amine (**P-2013**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),

(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),

(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),

(6-Methyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2079**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-2081**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2082**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methyl-pyridin-2-ylmethyl)-amine (**P-2131**),

[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2146**),

[3-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2147**),
(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2148**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2154**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine (**P-2163**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2172**),
Ethanesulfonic acid (2-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2198**),
Ethanesulfonic acid (3-fluoro-5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2202**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**, and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0103] In an eleventh aspect, a compound as described herein 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 is a compound selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-

ylmethyl)-amine (**P-1496**),
[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1622**),
N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1669**),
N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1679**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2001**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2028**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2030**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2043**),
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2045**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2052**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2057**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2062**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2063**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2064**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2067**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2070**),
(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2071**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2073**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2075**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2078**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2088**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2097**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-3-ylmethyl)-amine (**P-2103**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-4-ylmethyl)-amine (**P-2118**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2139**),
3-{[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-methyl}-5-fluoro-1-methyl-1H-pyridin-2-one (**P-2157**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2176**),
3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-2193**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-

3-yl]methyl]pyridin-2-amine **(P-2206)**, and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0104] In a twelfth aspect, a compound as described herein 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 protein kinases other than Flt-3, 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 dual Fms/Flt-3 inhibitor also inhibits Kit. In one embodiment, the dual Fms/Flt-3 inhibitor is a compound selected from the group consisting of:
(6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1644**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1646**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1667**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine (**P-2004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl)-amine (**P-2009**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2030**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),

(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),
(2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2034**),
(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2040**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2041**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2044**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2047**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2050**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2057**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**, and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0105] In one embodiment, the dual Fms/Flt-3 inhibitor is a compound selected from the group consisting of:
(6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-

pyridin-2-yl]-amine (**P-1644**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1646**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1667**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl)-amine (**P-2009**),
(2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2034**),
(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2040**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2041**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2044**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2047**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2050**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**, and
any salt, prodrug, tautomer, or stereoisomer thereof.

[0106] Further to any of the aspects and embodiments referred to herein, a compound as described herein also inhibits the effects of a mutation of the kinase (e.g. Fms mutant, Kit mutant, Flt-3 mutant), including, but not limited to, a mutation that is related to a disease state, such as a cancer.

[0107] In a thirteenth aspect, compositions are provided that include a therapeutically effective amount of any one or more compound(s) as described herein and at least one pharmaceutically

acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds as described herein. The composition can further include a plurality of different pharmacologically active compounds, which can include a plurality of compounds as described herein. In certain embodiments, the composition can include any one or more compound(s) as described herein along with one or more compounds that are therapeutically effective for the same disease indication. In one aspect, the composition includes any one or more compound(s) as described herein along with one or more compounds that are therapeutically effective for the same disease indication, wherein the compounds have a synergistic effect on the disease indication. In one embodiment, the composition includes any one or more compound(s) as described herein effective in treating a cancer and one or more other compounds that are effective in treating the same cancer, further wherein the compounds are synergistically effective in treating the cancer.

[0108] In a fourteenth aspect, methods are provided for modulating the activity of a Fms and/or Kit and/or Flt-3 protein kinase, including any mutations thereof, by contacting the protein kinase with an effective amount of any one or more compound(s) as described herein.

[0109] In a fifteenth aspect, the invention provides methods for treating a disease or condition mediated by Fms and/or Kit and/or Flt-3, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Fms and/or Kit, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0110] In a sixteenth aspect, the invention provides methods for treating a disease or condition mediated by Fms, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Fms, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0111] In a seventeenth aspect, the invention provides methods for treating a disease or condition mediated by Kit, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Kit, including any mutations thereof, in a subject in need thereof by administering to the

subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0112] In an eighteenth aspect, the invention provides methods for treating a disease or condition mediated by Flt-3, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Flt-3, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0113] In a nineteenth aspect, the invention provides methods for treating a disease or condition mediated by Fms and Flt-3, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Fms and Flt-3, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0114] In a twentieth aspect, the invention provides methods for treating a disease or condition mediated by Fms and Kit, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein. In one embodiment, the invention provides methods for treating a disease or condition mediated by Fms and Kit, including any mutations thereof, in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein in combination with one or more other suitable therapies for treating the disease.

[0115] In a twenty-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 a composition including any one or more compound(s) as described herein, in combination with one or more other therapies or medical procedures effective in treating the cancer. Other therapies or medical procedures include suitable anticancer therapy (e.g. drug therapy, vaccine therapy, gene therapy, photodynamic therapy) or medical procedure (e.g. surgery, radiation treatment, hyperthermia heating, bone marrow or stem cell transplant). In one embodiment, the one or more suitable anticancer therapies or medical procedures is selected from treatment with a chemotherapeutic agent (e.g. chemotherapeutic drug), radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam), hyperthermia heating

(e.g. microwave, ultrasound, radiofrequency ablation), Vaccine therapy (e.g. AFP gene hepatocellular carcinoma vaccine, AFP adenoviral vector vaccine, AG-858, allogeneic GM-CSF-secretion breast cancer vaccine, dendritic cell peptide vaccines), gene therapy (e.g. Ad5CMV-p53 vector, adenovector encoding MDA7, adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexafin lutetium), surgery, or bone marrow and stem cell transplantation.

[0116] In a twenty-second aspect, the invention provides a method of treating a cancer in a subject in need thereof by administering to the subject an effective amount of a composition including any one or more compound(s) as described herein, in combination with one or more suitable chemotherapeutic agents. In one embodiment, the one or more suitable chemotherapeutic agents is selected from an alkylating agent, including, but not limited to, adozelesin, altretamine, bendamustine, bizelesin, busulfan, carboplatin, carboquone, carmofur, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, etoglucid, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mannosulfan, mechlorethamine, melphalan, mitobronitol, nedaplatin, nimustine, oxaliplatin, piposulfan, prednimustine, procarbazine, ranimustine, satraplatin, semustine, streptozocin, temozolomide, thiotepa, treosulfan, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosphamide, and uramustine; an antibiotic, including, but not limited to, aclarubicin, amrubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, idarubicin, menogaril, mitomycin, neocarzinostatin, pentostatin, pirarubicin, plicamycin, valrubicin, and zorubicin; an antimetabolite, including, but not limited to, aminopterin, azacitidine, azathioprine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, tegafur-uracil, thioguanine, trimethoprim, trimetrexate, and vidarabine; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetan, ipilimumab, and tremelimumab; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, and tesetaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, demecolcine, homoharringtonine, vinblastine, vincristine, vindesine, vinflunine, and vinorelbine; an antiangiogenic agent, including, but not limited to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limited to, amsacrine, belotecan, edotecarin, etoposide, etoposide phosphate, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), lucanthone, mitoxantrone, pixantrone, rubitecan, teniposide, topotecan, and 9-aminocamptothecin; a kinase inhibitor, including, but not limited to, axitinib (AG 013736), dasatinib

(BMS 354825), erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, motesanib diphosphate (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, sunitinib malate, AEE-788, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib; a targeted signal transduction inhibitor including, but not limited to bortezomib, geldanamycin, and rapamycin; a biological response modifier, including, but not limited to, imiquimod, interferon-α, and interleukin-2; and other chemotherapeutics, including, but not limited to 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g. tanespimycin) and farnesyltransferase inhibitors (e.g. tipifarnib). Preferably, the method of treating a cancer involves administering to the subject an effective amount of a composition including any one or more compound(s) of Formulae I or I'in combination with a chemotherapeutic agent selected from capecitabine, 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, interferon-α, interleukin-2, or erlotinib.

[0117] In a twenty-third aspect, the invention provides a method of treating a disease or condition in a subject in need thereof, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically acceptable formulation of such compound or prodrug. The compound can be alone or can be part of a composition. In one embodiment, the invention provides a method of treating a disease or condition in a subject in need thereof, by administering to the subject a therapeutically effective amount of any one or more compound(s) as described herein, a prodrug of such compound, a pharmaceutically acceptable salt of such compound or prodrug, or a pharmaceutically acceptable formulation of such compound or prodrug in combination with one or more other suitable therapies for the disease or condition.

[0118] In a twenty-fourth aspect, the invention provides kits that include a compound or composition thereof as described herein. In some embodiments, the compound or composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the compound or composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the compound or composition is approved for administration to a mammal, e.g., a human, for a Fms and/or Kit 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 Fms and/or Kit 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.

[0119] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, the invention provides methods for treating a Kit-mediated disease or condition in a subject in need thereof (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal Kit activity (e.g. kinase activity). In some embodiments invention methods may involve administering to the subject suffering from or at risk of a c-kit-mediated disease or condition an effective amount of one or more compound(s) as described herein. In one embodiment, the Kit mediated disease 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, 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, 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.

[0120] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, the invention provides methods for treating a Fms-mediated disease or condition in a subject in need thereof (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal Fms activity (e.g. kinase activity). In some embodiments, invention methods may involve administering to the subject suffering from or at risk of a Fms-mediated disease or condition an effective amount of one or more compound(s) as described herein. In one embodiment, the Fms mediated disease 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), myclopreparation 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, metastasis of tumors to other tissues, osteolytic bone metastases, 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.

[0121] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, the invention provides methods for treating a disease or condition mediated by Fms and Kit in a subject in need thereof (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal Fms activity and 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 mediated by Fms and Kit an effective amount of one or more compound(s) as described herein. In one embodiment, the condition mediated by Fms and Kit is selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, allergy, anaphylaxis, asthma, allergic rhinitis, ankylosing spondylitis, polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis, Still's disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, immune thrombocytopenic purpura, myelopreparation for autologous transplantation, transplant rejection, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome, multicentric reticulohistiocytosis, hypereosinophilia, and urticaria type I diabetes, type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis, and peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, nephritis, tubular necrosis, diabetes-associated renal complications, and renal hypertrophy, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease, acute pain, neuropathic pain, inflammatory pain, chronic pain, migraine, multiple myeloma, acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, mast cell tumors, canine mast cell tumors, lung cancer, testicular cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, merkel cell carcinoma, carcinomas of the female genital tract, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors, tumor angiogenesis, astrocytoma, neuroblastoma, sarcoma, osteosarcoma, sarcomas of neuroectodermal origin, giant cell tumor of bone, giant cell tumor of tendon sheath, pigmented villonodular synovitis, melanoma, glioblastoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), mastocytosis, metastasis of tumors to other tissues, osteolytic bone metastases, and other chronic myeloproliferative diseases such as myelofibrosis, collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis, uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy, cherubism, neurofibromatosis, infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis, Gaucher's disease,

Fabry's disease, Niemann-Pick disease, liver cirrhosis, gastroesophageal reflux disease, esophagitis, and gastrointestinal tract ulcers, pulmonary fibrosis, acute lung injury, bypass surgery, vascular surgery, and vascular grafts, atherosclerosis, cardiomyopathy, heart failure, and pulmonary arterial hypertension.

[0122] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, the invention provides methods for treating a disease or condition mediated by Fms and Flt-3 in a subject in need thereof (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal Fms activity and 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 mediated by Fms and Flt-3 an effective amount of one or more compound(s) as described herein. In one embodiment, the condition mediated by Fms and Flt-3 is acute myeloid leukemia.

[0123] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein 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, 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, metastatic 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.

[0124] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein 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, wherein the compound is an inhibitor of Kit, i.e. 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 Kit kinase activity assay.

[0125] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, and renal hypertrophy, wherein the compound is a Fms selective inhibitor, i.e. 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 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.

[0126] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, and Parkinson's disease, wherein the compound is a Fms selective inhibitor, i.e. 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 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, and wherein the compound effectively crosses the blood brain barrier; in some embodiments, the compound is also selective relative to protein kinase 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.

[0127] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein 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, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, and renal hypertrophy, wherein the compound is a Fms selective inhibitor, i.e. 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 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, and wherein the compound does not effectively cross the blood brain barrier; in some embodiments, the compound is also selective relative to protein kinase 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.

[0128] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein to a subject in need thereof suffering from or at risk of a disease or condition selected from the group consisting of metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis, wherein the compound is a dual Fms/Kit inhibitor, i.e. 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 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 also selective relative to protein kinase 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 CSK, Insulin receptor kinase, AMPK, PDGFR or VEGFR.

[0129] In aspects and embodiments involving treatment of a disease or condition with one or more of the compounds described herein, invention methods may involve administering an effective amount of one or more compound(s) as described herein to a subject in need thereof suffering from or at risk of acute myeloid leukemia, wherein the compound is a dual Fms/Flt-3 inhibitor, i.e. 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 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 also selective relative to protein kinase other than Flt-3, 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.

[0130] In a twenty-fifth aspect, one or more compounds or compositions as described herein can be used in the preparation of a medicament for the treatment of a Kit-mediated disease or condition selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, non-small cell lung cancer, 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, tumor angiogenesis, 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, esophagitis, and gastrointestinal tract ulcers; ophthalmic indications, including but not limited to uveitis and retinitis; and neurologic indications, including but not limited to migraine. The invention further provides one or more compounds or compositions as described herein for use in treating a Kit-mediated disease or condition as described herein.

[0131] In a twenty-sixth aspect, one or more compounds as described herein can be used in the preparation of a medicament for the treatment of a Fms-mediated disease or condition 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, metastasis of tumors to other tissues, osteolytic bone metastases, 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. The invention further provides one or more compounds or compositions as described herein for use in treating a Fms-mediated disease or condition as described herein.

[0132] In a twenty-seventh aspect, one or more compounds as described herein can be used in the preparation of a medicament for the treatment of a Fms-mediated and Kit-mediated disease or condition selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, dermatitis, allergy, anaphylaxis, asthma, allergic rhinitis, ankylosing spondylitis,

polymyositis, dermatomyositis, systemic sclerosis, juvenile idiopathic arthritis, polymyalgia rheumatica, Sjogren's disease, Langerhan's cell histiocytosis, Still's disease, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, immune thrombocytopenic purpura, myelopreparation for autologous transplantation, transplant rejection, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome, multicentric reticulohistiocytosis, hypereosinophilia, and urticaria type I diabetes, type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis, osteoporosis, osteodystrophy, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis, and peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, nephritis, tubular necrosis, diabetes-associated renal complications, and renal hypertrophy, multiple sclerosis, Charcot Marie Tooth syndrome, amyotrophic lateral sclerosis, myasthenia gravis, chronic demyelinating polyneuropathy, other demyelinating disorders, stroke, Alzheimer's disease and Parkinson's disease, acute pain, neuropathic pain, inflammatory pain, chronic pain, migraine, multiple myeloma, acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, mast cell tumors, canine mast cell tumors, lung cancer, testicular cancer, pancreatic cancer, prostate cancer, breast cancer, ovarian cancer, merkel cell carcinoma, carcinomas of the female genital tract, colorectal carcinoma, carcinoma in situ, gastrointestinal stromal tumors, tumor angiogenesis, astrocytoma, neuroblastoma, sarcoma, osteosarcoma, sarcomas of neuroectodermal origin, giant cell tumor of bone, giant cell tumor of tendon sheath, pigmented villonodular synovitis, melanoma, glioblastoma, glioblastoma multiforme, glioma, other tumors of the central nervous system, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), mastocytosis, metastasis of tumors to other tissues, osteolytic bone metastases, and other chronic myeloproliferative diseases such as myelofibrosis, collagen vascular disease, polyarteritis nodosa, Behcet's disease, sarcoidosis, familiar Mediterranean fever, Churg-Strauss vasculitis, temporal arteritis, giant cell arteritis, Takayasu's arteritis, uveitis, scleritis, retinitis, age related macular degeneration, choroidal neovascularization, diabetic retinopathy, cherubism, neurofibromatosis, infections associated with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human granulocytic anaplasmosis, Gaucher's disease, Fabry's disease, Niemann-Pick disease, liver cirrhosis, gastroesophageal reflux disease, esophagitis, and gastrointestinal tract ulcers, pulmonary fibrosis, acute lung injury, bypass surgery, vascular surgery, and vascular grafts, atherosclerosis, cardiomyopathy, heart failure, and pulmonary arterial hypertension. The invention further provides one or more compounds or compositions as described herein for use in treating a a Fms-mediated and Kit-mediated disease or condition as described herein.

[0133] In a twenty-eighth aspect, one or more compounds as described herein 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, ulcerative colitis, Crohn's disease, immune thrombocytopenic purpura, 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, metastatic 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.

[0134] In a twenty-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.

[0135] In a thirtieth 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, glioblastoma, Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, or renal hypertrophy.

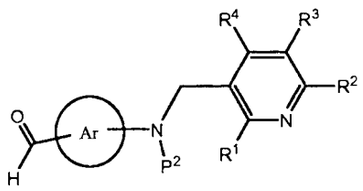
[0136] In a thirty-first aspect, one or more compounds as described herein that are Fms selective inhibitors that effectively cross the blood brain barrier can be used in the preparation of a medicament for the treatment of multiple sclerosis, glioblastoma, Alzheimer's disease, or Parkinson's disease.

[0137] In a thirty-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, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, or renal hypertrophy.

[0138] In a thirty-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 metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis.

[0139] In a thirty-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 acute myeloid leukemia.

[0140] In a thirty-fifth aspect, the invention provides an intermediate compound of Formula V:



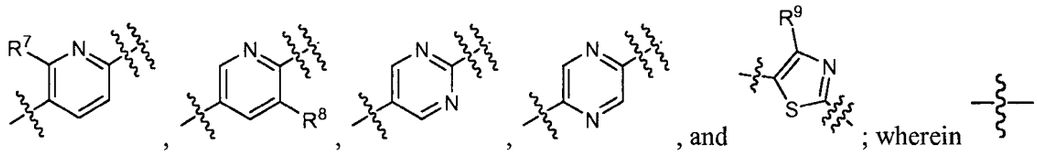
Formula V

or a stereoisomer thereof,

wherein:

P^2 is an amino protecting group;

Ar is selected from the group consisting of:



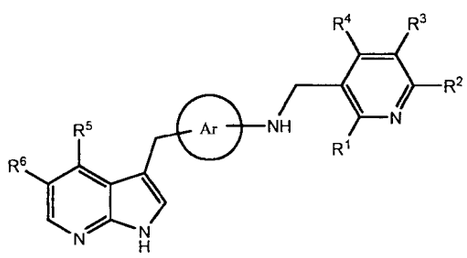
, and ; wherein indicates the point of attachment of Ar to $-CH_2-$ of Formula I and wherein indicates the point of attachment of Ar to -NH- of Formula I;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of –H, halogen, lower alkyl, halogen substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, and $-N(H)-S(O)_2-R^{43}$, provided that at least two of R^1, R^2, R^3 and R^4 are –H and one of R^1, R^2, R^3 and R^4 is other than hydrogen, wherein:

R^{40} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

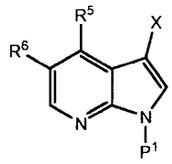
R^{41}, R^{42} and R^{43} are lower alkyl. In some embodiments, the variables Ar, R^7, R^8, R^9, R^1, R^2, R^3 and R^4 are as defined herein.

[0141] In a thirty-sixth aspect, the invention provides a method for preparing a compound of Formula I':



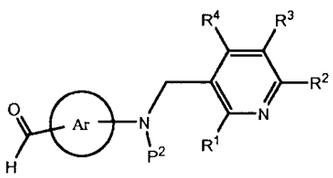
Formula I'

The method includes contacting a compound of Formula IV:



Formula IV

with a compound of Formula V:



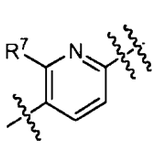
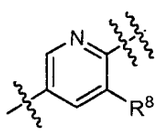
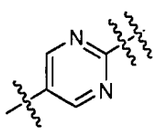
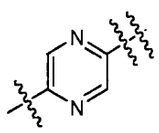
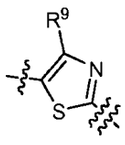
Formula V

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

P^1 and P^2 are each independently an amino protecting group;

X is H or a halogen;

Ar is selected from the group consisting of:

 ,  ,  ,  , and  ; wherein 

indicates the point of attachment of Ar to $-CH_2-$ of Formula I and wherein  indicates the point of attachment of Ar to -NH- of Formula I;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of –H, lower alkyl, halogen substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, and $-N(H)-S(O)_2-R^{43}$, provided that at least two of R^1, R^2, R^3 and R^4 are –H and one of R^1, R^2, R^3 and R^4 is other than hydrogen, wherein:

R^{40} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{41}, R^{42} and R^{43} are lower alkyl;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$,

-C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is H, halogen or lower alkyl;

R^8 is H, halogen, lower alkyl or lower alkoxy;

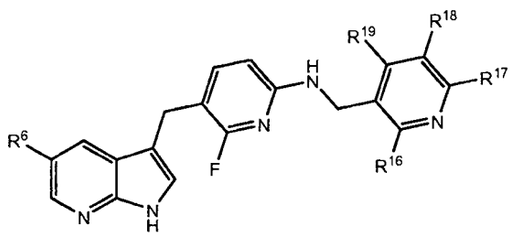
R^9 is H or halogen;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH_3, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

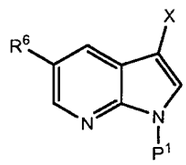
R^{12} and R^{15} are each independently lower alkyl, with the proviso that the compound is other than those set forth in Table 1. P^1 and P^2 are amino protecting groups as described herein. In one embodiment, P^2 is t-butoxycabonyl. In another embodiment, P^1 is phenylsulfonyl. In one embodiment, the contacting is performed by reacting the compounds of Formula IV with the compounds of Formula V in the presence of a strong base, such as alkali metal hydroxide. Exemplary alkali metal hydroxides include NaOH, KOH and LiOH. In another embodiment, the contacting includes forming a Grignard reagent of compounds of Formula IV and further reacting the Grignard reagent of compounds of Formula IV with the compounds of Formula V. In yet another embodiment, the contacting includes reacting the compounds of Formula IV with the compounds of Formula V in the presence of a palladium complex. In some embodiments, the variables R^5 and R^6 are as defined in any of the embodiments above for compounds of Formula I. In some embodiments, the variables R^1, R^2, R^3 and R^4 are as defined in any of the embodiments above for compounds of Formula I.

[0142] In some embodiments, the invention provides a method of preparing a compound of Formula II':



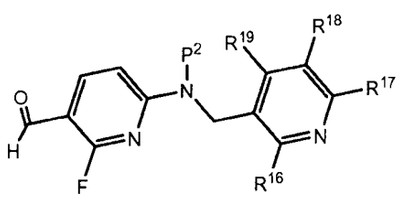
Formula II'

The method includes contacting a compound of Formula VI:



Formula VI

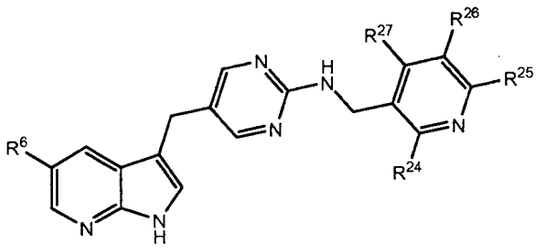
with a compound of Formula VII:



Formula VII

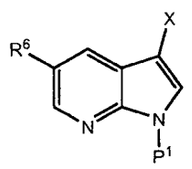
under conditions sufficient to form the compound of Formula II', wherein P^1 and P^2 are each independently an amino protecting group; X is H or a halogen; R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl. In one embodiment, R^6 is lower alkyl. In another embodiment, R^6 is CH_3 or CN. In another embodiment, R^6 is methyl, ethyl or propyl. P^1 and P^2 are amino protecting groups as described herein. In one embodiment, P^2 is t-butoxycabonyl. In another embodiment, P^1 is phenylsulfonyl. In one embodiment, the contacting is performed by reacting the compounds of Formula VI with the compounds of Formula VII in the presence of a strong base, such as alkali metal hydroxide. Exemplary alkali metal hydroxide include NaOH, KOH and LiOH. In another embodiment, the contacting includes forming a Grignard reagent of compounds of Formula VI and further reacting the Grignard reagent of compounds of Formula VI with the compounds of Formula VII.

[0143] In some embodiments, the invention provides a method of preparing a compound of Formula III':



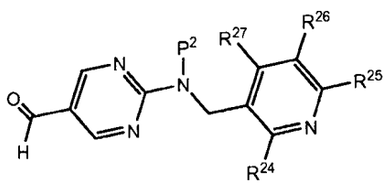
Formula III'

The method includes contacting a compound of Formula VI:



Formula VI

with a compound of Formula VII:



Formula VIII

under conditions sufficient to form the compound of Formula II', wherein P^1 and P^2 are each independently an amino protecting group; X is H or a halogen; R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl. R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl. In one embodiment, R^6 is lower alkyl. In another embodiment, R^6 is CH_3 or CN. In another embodiment, R^6 is methyl, ethyl or propyl. P^1 and P^2 are amino protecting groups as described herein. In one embodiment, P^2 is t-butoxycabonyl. In another embodiment, P^1 is phenylsulfonyl. In one embodiment, the contacting is performed by reacting the compounds of Formula VI with the compounds of Formula VIII in the presence of a strong base, such as alkali metal hydroxide. Exemplary

alkali metal hydroxide include NaOH, KOH and LiOH. In another embodiment, the contacting includes forming a Grignard reagent of compounds of Formula VI and further reacting the Grignard reagent of compounds of Formula VI with the compounds of Formula VII.

[0144] Additional aspects and embodiments will be apparent from the following Detailed Description of the Invention and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0145] As used herein the following definitions apply unless clearly indicated otherwise:

[0146] 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.

[0147] "Halogen" or "Halo" refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0148] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. A lower alkyl may be independently substituted as described herein, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, wherein the substituents are as indicated. Furthermore, possible substitutions are attached at any available atom to produce a stable compound. For example "halo substituted lower alkyl" denotes a lower alkyl group substituted with one or more halogen atoms, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 halogen atoms, also 1, 2, or 3 halogen atoms. Furthermore, possible substitutions are attached at any available atom to produce 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 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. Exemplary fluoro

substituted lower alkyl includes, but is not limited to, CF_3, CF_2CF_3, CH_2CF_3, and the like. It is understood that substitutions are chemically feasible and attached at any available atom to provide a stable compound.

[0149] "Lower alkoxy" refers to those lower alkyl groups as defined herein attached to the remainder of the molecule via an oxygen atom. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, n-pentoxy, n-heptoxy, and the like, as well as isomers thereof.

[0150] "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. The straight chain or branched lower alkenyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like.

[0151] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. The straight chain or branched lower alkynyl group is chemically feasible and attached at any available point to provide a stable compound. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like.

[0152] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

[0153] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which a ring carbon may be oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl.

[0154] "Cycloalkylamino" denotes the group -NR^aR^b, where R^a and R^b combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with lower alkyl. Examples of 5-7 membered heterocycloalkyl include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. It is understood that when cycloalkylamino is a substituent on other moieties, these are chemically feasible and attached at any available atom to provide a stable compound.

[0155] As used herein "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), tri-isopropylsilyl (TIPS), phenylsulphonyl and the like (see also, Boyle, A. L. (Editor), CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000).

[0156] As used herein, "Leaving 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.

[0157] 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.

[0158] As used herein, the term "Fms and/or Kit protein kinase mediated 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 protein kinase mediated disease or condition includes a disease or condition for which modulation provides a

therapeutic benefit, e.g. wherein treatment with Fms and/or Kit protein kinase inhibitor(s), including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0159] As used herein, the terms "Fms protein kinase mediated disease or condition," "c-fms mediated disease or condition," and the like refer 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 protein kinase mediated disease or condition includes a disease or condition for which Fms inhibition provides a therapeutic benefit, e.g. wherein treatment with Fms inhibitor(s), including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0160] As used herein, the terms "Kit protein kinase mediated disease or condition," "c-kit mediated disease or condition," and the like refer 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 protein kinase mediated disease or condition includes a disease or condition for which Kit inhibition provides a therapeutic benefit, e.g. wherein treatment with Kit inhibitor(s), including one or more compound(s) described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0161] 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 protein kinase mediated and Kit protein kinase mediated 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 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 protein kinase mediated disease or condition, the dual inihibition of Fms and Kit provides beneficial effects in treating certain diseases or conditions, including, but not limited to, metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, or multiple sclerosis.

[0162] 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 protein kinase mediated and Flt-3 protein kinase mediated 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 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 protein kinase 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, acute myeloid leukemia.

[0163] 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 protein kinase mediated disease or condition, the Fms selectivity provides beneficial effects in treating certain diseases or conditions, including, but not limited to, rheumatoid arthritis, Alzheimer's disease, Parkinson's disease, osteoarthritis, nephritis, diabetic nephropathy, or renal hypertrophy.

[0164] 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 protein kinase mediated 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, glioblastoma, Alzheimer's disease, and Parkinson's disease, 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, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis,diabetic nephropathy, or renal hypertrophy.

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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).

[0170] 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.

[0171] As used herein, the term "composition" refers to a pharmaceutical preparation suitable for administration to an intended subject for therapeutic purposes that contains at least one pharmaceutically active compound, including any solid form thereof. The composition may include at least one pharmaceutically acceptable component to provide an improved formulation of the compound, such as a suitable carrier or excipient.

[0172] As used herein, the term "subject" refers to a living organism that is treated with compounds as described herein, including, but not limted to, any mammal, such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats.

[0173] As used herein, the term "biopharmaceutical properties" refers to the pharmacokinetic action of a a compound or complex of the present invention, including the dissolution, absorption and distribution of the compound on administration to a subject. As such, certain solid forms of compounds of the invention, such as amorphous complexes of compounds of the invention, are intended to provide improved dissolution and absorption of the active compound, which is typically reflected in improved C_{max} (i.e. the maximum achieved concentration in the plasma after administration of the drug) and improved AUC (i.e. area under the curve of drug plasma concentration vs. time after administration of the drug).

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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 can be assayed based on its ability to bind to a particular target molecule or molecules.

[0179] 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 inhibitor of a particular biomolecule modulates the activity of that

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

[0180] 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.

[0181] "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

[0182] 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, i.e. Fms kinase and Kit kinase, contemplated by the present invention are described in the art, including, without limitation, 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:

[0183] **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.

[0184] 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.

[0185] 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).

[0186] 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 myclomonocytic leukemia and AML type M4 (23%), both of which are characterized by monocytic differentiation.

[0187] 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.

[0188] 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.

[0189] 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).

[0190] Atherosclerosis, an inflammatory disease of the vessel walls, is associated with significant morbidity and mortality. A 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.

[0191] 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.

[0192] 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. Fms is also a target for

amelioration of metastatic breast cancer (Lawicki et al., Clin Chim Acta. 2006, Sep, 371(1-2):112-6; Wyckoff et al., Cancer Res. 2007, Mar 15, 67(6):2649-56).

[0193] 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.

[0194] 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.

[0195] 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.

[0196] Insulin resistance and obesity are hallmark of type II diabetes and there is a strong correlation between insulin resistance and abdominal visceral fact 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.

[0197] 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.

[0198] A Fms inhibitor 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.

[0199] **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.

[0200] 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, Hematol 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.

[0201] 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.

[0202] 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).

[0203] 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). Kit inihibitors can also be used to target melanoma (Smalley et al., Histol Histopathol. 2009, May, 24(5):643-50), gastrointestinal stromal tumors (Demetri, GD, Semin Oncol. 2001, Oct, 28(5 Suppl 17):19-26), neurofibromatosis (Yang et al., Cell, 2008, Oct 31, 135(3):437-48), and multiple sclerosis (Secor et al., J Exp Med. 2000, Mar 6, 191(5):813-22).

[0204] A Kit inhibitor 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, neurofibromatosis (including Schwann cell neoplasia associated with neurofibromatosis), 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 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 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.

[0205] **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).

[0206] 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.

Kinase Activity Assays

[0207] 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 of kinases. In addition to the assays mentioned in the Examples below, one of ordinary skill in the art can readily identify 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.

[0208] 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

[0209] 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

[0210] 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

[0211] 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.

[0212] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Esters include, for example, esters of a carboxylic acid group, or S-acyl or O-acyl derivatives of thiol, alcohol, or phenol groups. In this context, a common example is an alkyl ester of a carboxylic acid. Prodrugs may also include variants wherein an -NH group of the compound has undergone acylation, such as the 7-position of the pyrrolo[2,3-d]pyrimidine ring or the 1-position of the 1H-pyrrolo[2,3-b]pyridine ring of compounds as described herein, where cleavage of the acyl group provides the free -NH group of the active drug. Some prodrugs are activated enzymatically to yield the active compound, or a compound may undergo further chemical reaction to yield the active compound. Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0213] 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:

[0214] 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.

[0215] 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.

[0216] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation to 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.

[0217] 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*.

[0218] 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.

[0219] 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

[0220] 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.

[0221] Likewise, some of the compounds according to the present invention may exist as stereoisomers, i.e. having the same atomic connectivity of covalently bonded atoms yet differing in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g.

enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*-orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Unless specified to the contrary, all such steroisomeric forms are included within the formulae provided herein.

[0222] 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

[0223] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound. Thus, compounds described herein can be in the form of pharmaceutically acceptable salts, or can be formulated as pharmaceutically acceptable salts. Contemplated pharmaceutically acceptable salt forms include, without limitation, mono, bis, tris, tetrakis, and so on. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0224] 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.

[0225] 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.

[0226] 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

[0227] 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.

[0228] 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, malcate, 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.

[0229] 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, DMSO, ethyl acetate, acetic acid, or ethanolamine.

Formulations and Administration

[0230] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. Compounds described herein can be administered by different routes, including injection (i.e. parenteral, including intravenous, intraperitoneal, subcutaneous, and intramuscular), oral, transdermal, transmucosal, rectal, or inhalant. Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations generally may be found in Remington: *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0231] In some embodiments, compositions will comprise pharmaceutically acceptable carriers or excipients, such as fillers, binders, disintegrants, glidants, lubricants, complexing agents, solubilizers, and surfactants, which may be chosen to facilitate administration of the compound by a particular route. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, types of starch, cellulose derivatives, gelatin, lipids, liposomes, nanoparticles, and the like. Carriers also include physiologically compatible liquids as solvents or for suspensions, including, for example, sterile solutions of water for injection (WFI), saline solution, dextrose solution, Hank's solution, Ringer's solution, vegetable oils, mineral oils, animal oils, polyethylene glycols, liquid paraffin, and the like. Excipients may also include, for example, colloidal silicon dioxide, silica gel, talc, magnesium silicate, calcium silicate, sodium aluminosilicate, magnesium trisilicate, powdered cellulose, macrocrystalline cellulose, carboxymethyl cellulose, cross-linked sodium carboxymethylcellulose, sodium benzoate, calcium carbonate, magnesium carbonate, stearic acid, aluminum stearate, calcium stearate, magnesium stearate, zinc stearate, sodium stearyl fumarate, syloid, stearowet C, magnesium oxide, starch, sodium starch glycolate, glyceryl monostearate, glyceryl dibehenate, glyceryl palmitostearate, hydrogenated vegetable oil, hydrogenated cotton seed oil, castor seed oil mineral oil, polyethylene glycol (e.g. PEG 4000-8000), polyoxyethylene glycol, poloxamers, povidone, crospovidone, croscarmellose sodium, alginic acid, casein, methacrylic acid divinylbenzene copolymer, sodium docusate, cyclodextrins (e.g. 2-hydroxypropyl-.delta.-cyclodextrin), polysorbates (e.g. polysorbate 80), cetrimide, TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate), magnesium lauryl sulfate, sodium lauryl sulfate, polyethylene glycol ethers, di-fatty acid ester of polyethylene glycols, or a polyoxyalkylene sorbitan fatty acid ester (e.g., polyoxyethylene sorbitan ester Tween®), polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid ester, e.g. a sorbitan fatty acid ester from a fatty acid such as oleic, stearic or palmitic acid, mannitol, xylitol, sorbitol, maltose, lactose, lactose monohydrate or lactose spray dried, sucrose, fructose, calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, dextrates, dextran, dextrin, dextrose, cellulose acetate, maltodextrin, simethicone,

polydextrosem, chitosan, gelatin, HPMC (hydroxypropyl methyl celluloses), HPC (hydroxypropyl cellulose), hydroxyethyl cellulose, and the like.

[0232] In some embodiments, oral administration may be used. Pharmaceutical preparations for oral use can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops. Compounds described herein may be combined with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain, for example, tablets, coated tablets, hard capsules, soft capsules, solutions (e.g. aqueous, alcoholic, or oily solutions) and the like. Suitable excipients are, in particular, fillers such as sugars, including lactose, glucose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, corn starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone); oily excipients, including vegetable and animal oils, such as sunflower oil, olive oil, or codliver oil. The oral dosage formulations may also contain disintegrating agents, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate; a lubricant, such as talc or magnesium stearate; a plasticizer, such as glycerol or sorbitol; a sweetening such as sucrose, fructose, lactose, or aspartame; a natural or artificial flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring; or dye-stuffs or pigments, which may be used for identification or characterization of different doses or combinations. Also provided are dragee cores with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

[0233] 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.

[0234] In some embodiments, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. Compounds described herein for injection may be formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. Dispersions may also be prepared in non-aqueous solutions, such as glycerol, propylene glycol, ethanol, liquid polyethylene glycols, triacetin, and vegetable oils. Solutions may also contain a preservative, such as methylparaben, propylparaben, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In addition, the

compounds may be formulated in solid form, including, for example, lyophilized forms, and redissolved or suspended prior to use.

[0235] In some embodiments, transmucosal, topical or transdermal administration may be used. In such formulations of compounds described herein, penetrants appropriate to the barrier to be permeated are used. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal). Compositions of compounds described herein for topical administration may be formulated as oils, creams, lotions, ointments, and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). In some embodiments, carriers are selected such that the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of solvent (e.g., an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will be continuous rather than intermittent throughout the dosage regimen.

[0236] In some embodiments, compounds are administered as inhalants. Compounds described herein may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds described herein may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone proprionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratroprium bromide or tiotropium; vasodilators such as treprostinal and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0237] 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.

[0238] The compounds described herein may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. In some embodiments, dosage may be modified for one or more of the compounds of the invention or other therapeutics used in combination, e.g., reduction in the amount dosed relative to a compound or therapy used alone, by methods well known to those of ordinary skill in the art.

[0239] It is understood that use in combination includes use with other therapies, drugs, medical procedures etc., where the other therapy or procedure may be administered at different times (e.g. within a short time, such as within hours (e.g. 1, 2, 3, 4-24 hours), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks)) than a compound described herein, or at the same time as a compound described herein. Use in combination also includes use with a therapy or medical procedure that is administered once or infrequently, such as surgery, along with a compound described herein administered within a short time or longer time before or after the other therapy or procedure. In some embodiments, the present invention provides for delivery of a compound described herein and one or more other drug therapeutics delivered by a different route of administration or by the same route of administration. The use in combination for any route of administration includes delivery of a compound described herein and one or more other drug therapeutics delivered by the same route of administration together in any formulation, including formulations where the two compounds are chemically linked in such a way that they maintain their therapeutic activity when administered. In one aspect, the other drug therapy may be co-administered with a compound described herein. Use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g. within an hour, 2 hours, 3 hours, up to 24 hours), administered by the same or different routes. Co-administration of separate formulations includes co-administration by delivery via one device, for example the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. Co-formulations of a compound described herein and one or more additional drug therapies delivered by the same route includes preparation of the materials together such that they can be

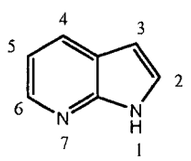
administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that they are chemically joined, yet still maintain their biological activity. Such chemically joined compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

EXAMPLES

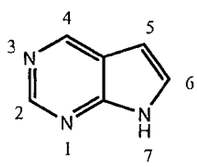
[0240] Examples related to the present invention are described below. In most cases, alternative techniques can be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. In some examples, the mass spectrometry result indicated for a compound 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. Compounds in the following examples are characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

[0241] 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.

[0242] Ring numbering for the 1H-pyrrolo[2,3-b]pyridine in the following Examples is as follows:



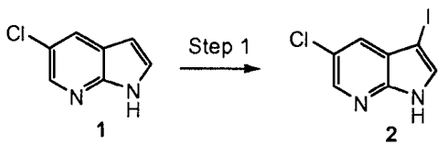
[0243] Ring numbering for the 7H-pyrrolo[2,3-d]pyrimidine in the following Examples is as follows:



Example 1: Synthesis of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine 2.

[0244] 5-Chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** was prepared in one step from 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 1.

Scheme 1



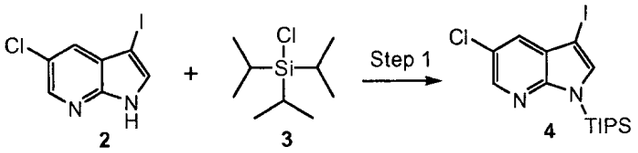
Step 1 – Preparation of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (2):

[0245] 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 nitrogen, pyridine (7.951 mL, 98.31 mmol) and iodine monochloride (110 mL, 1.0 M in dichloromethane, 110 mmol) were added slowly over 20 minutes. The reaction was stirred at room temperature for 2 hours, then quenched with 100 mL of 1 M aqueous sodium thiosulfate pentahydrate. The layers were separated, solids collected from the aqueous layer by filtration and combined with the organic layer. The aqueous layer was extracted with ethyl acetate, organic layers were combined and washed with brine, then concentrated under vacuum. The resulting solid was washed with 20% ethyl acetate in hexane to provide the desired compound. 5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine is prepared similarly from 5-fluoro-1H-pyrrolo[2,3-b]pyridine.

Example 2: Synthesis of 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine 4.

[0246] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **4** was prepared in one step from 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** as shown in Scheme 2.

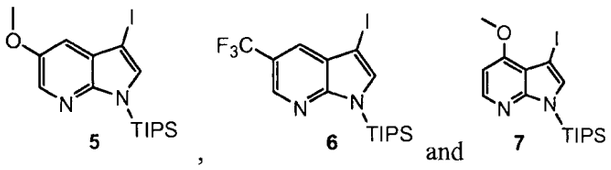
Scheme 2



Step 1 – Preparation of 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (4):

[0247] 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, 60% in mineral oil, 77.5 mmol) was added. The reaction was stirred at room temperature for 90 minutes, then triisopropysilyl chloride (**3**, 13.00 mL, 61.36 mmol) was added slowly. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**4**, 10.0 g). 5-fluoro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine is prepared similarly from 5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine.

[0248] 3-Iodo-5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **5**, 3-iodo-5-trifluoromethyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **6**, and 3-iodo-4-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **7**

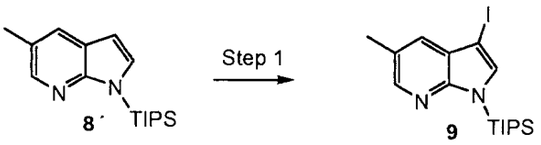


are prepared similarly to the protocol of Scheme 2, replacing 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** with 3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine, 3-iodo-5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridine, and 3-iodo-4-methoxy-1H-pyrrolo[2,3-b]pyridine, respectively. MS (ESI) $[M+H^+]^+ = 431.2$ (compound **5**) and 469.4 (compound **6**).

Example 3: Synthesis of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine 9.

[0249] 3-Iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **9** was prepared in one step from 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** as shown in Scheme 3.

Scheme 3



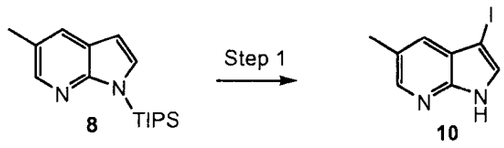
Step 1 – Preparation of 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (9):

[0250] 5-Methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**, 1.1 g, 3.8 mmol) and 10 mL of dichloromethane were 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 was added and stirred at room temperature overnight. The reaction was quenched with sodium thiosulfate (20 mL, 1M in water) and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried with sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate and hexanes. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a light yellow oil (**9**, 1.2 g, 75%). MS (ESI) $[M+H^+]^+ = 415.08$.

Example 4: Synthesis of 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine 10.

[0251] 3-Iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **10** was prepared in one step from 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **8** as shown in Scheme 4.

Scheme 4



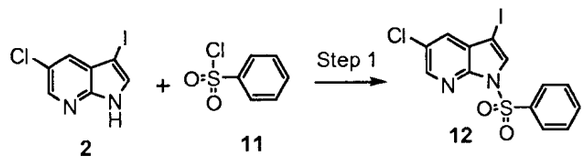
Step 1 – Preparation of 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine (10):

[0252] To a solution of 5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**8**, 1 g, 2.0 mmol) in 10 mL of tetrahydrofuran, iodine (0.43 g, 1.7 mmol) in 5 mL of tetrahydrofuran was added. The reaction was stirred at room temperature overnight, then quenched with 20 mL of 1M aqueous sodium thiosulfate and extracted with ethyl acetate. The organic layers were combined and washed with water, brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate and hexanes. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a white solid (**10**, 20 mg). MS (ESI) $[M+H^+]^+ = 258.70$.

Example 5: Synthesis of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine 12.

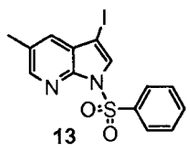
[0253] 1-Benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **12** was prepared in 1 step from 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** and benzenesulfonyl chloride **11** as shown in Scheme 5.

Scheme 5



Step 1 – Preparation of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (12):

[0254] To a solution of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**2**, 5.00 g, 18.0 mmol) in 80.0 mL of N,N-dimethylformamide, sodium hydride (1.1 g, 60% in mineral oil, 27.0 mmol) was added slowly. A solution of benzenesulfonyl chloride (**11**, 2.40 mL, 18.8 mmol) in 10.0 mL of N,N-dimethylformamide was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 15 hours, then poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting solid was washed with 5% ethyl acetate in hexane, isolated by filtration, and dried to provide the desired compound (**12**, 5.9 g). ^{1}H NMR was consistent with the compound structure. 1-Benzenesulfonyl-3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **13**



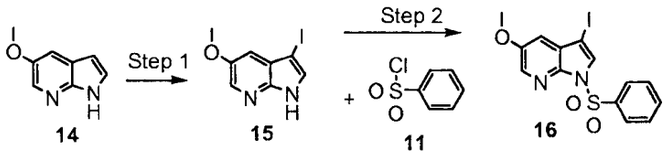
13

was prepared similarly to this protocol, replacing 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **2** with 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine **10**. 1-Benzenesulfonyl-5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine is prepared similarly from 5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine.

Example 6: Synthesis of 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine 16.

[0255] 1-Benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **16** was prepared in two steps from 5-methoxy-1H-pyrrolo[2,3-b]pyridine **14** as shown in Scheme 6.

Scheme 6



Step 1 – Preparation of 3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (15):

[0256] To a solution of 5-methoxy-1H-pyrrolo[2,3-b]pyridine (**14**, 300 mg, 2.0 mmol) in 30 mL of dichloromethane under nitrogen, iodine monochloride (3 mL, 1.0 M in dichloromethane, 3.0 mmol) was added at -40 °C. The reaction was stirred to room temperature, then quenched with 10 mL of 1 M aqueous sodium thiosulfate pentahydrate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with water, brine, then dried over sodium sulfate, decolored with activated carbon, filtered and the filtrate concentrated under vacuum. The resulting solid was washed with 20% ethyl acetate in hexane to provide the desired compound (**15**, 371 mg). MS (ESI) $[M+H^+]^+ = 275.03$.

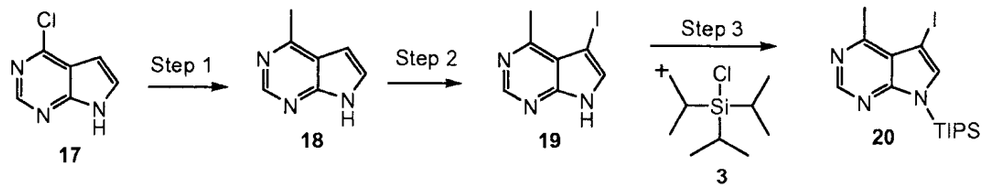
Step 2 – Preparation of 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (16):

[0257] To a solution of 3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**15**, 4.30 g, 15.7 mmol) in 53.6 mL of N,N-dimethylformamide under nitrogen, sodium hydride (0.690 g, 60% in mineral oil, 17.2 mmol) was added. After 10 minutes, benzenesulfonyl chloride (**11**, 2.20 mL, 17.2 mmol) was added and the reaction was cooled in a water bath. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate purified by silica gel column chromatography, eluting with 30-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**16**, 4.60 g).

Example 7: Synthesis of 5-iodo-4-methyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine 20.

[0258] 5-Iodo-4-methyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine **20** was prepared in two steps from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **17** as shown in Scheme 7.

Scheme 7



Step 1 – Preparation of 4-methyl-7H-pyrrolo[2,3-d]pyrimidine (18):

[0259] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**17**, 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) was added under nitrogen. After stirring for 10 minutes, methylmagnesium bromide (62.9 mL, 3.00 M in ether, 189 mmol) was added slowly. The reaction was heated at 55 °C overnight, then cooled to -70 to -80 °C and quenched by adding ammonium chloride dropwise. Then 1N hydrochloric acid was added and the pH was adjusted to 7-8 with addition of saturated sodium bicarbonate. This was extracted 3x with ethyl acetate. The combined organic layer was washed with saturated ammonium chloride and brine, then dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate and dichloromethane, then methanol and dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a tan solid (**18**). MS (ESI) $[M+H^+]^+ = 134$.

Step 2 – Preparation of 5-iodo-4-methyl-7H-pyrrolo[2,3-d]pyrimidine (19):

[0260] To 4-methyl-7H-pyrrolo[2,3-d]pyrimidine (**18**, 0.634 g, 4.76 mmol) in 50 mL of dichloromethane, N-iodosuccinimide (1.3 g, 5.7 mmol) was added and the reaction stirred at room temperature for 45 minutes. The reaction was concentrated under vacuum, then ethyl acetate was added and washed with 1 N aqueous sodium thiosulfate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**19**, 0.94 g). MS (ESI) $[M+H^+]^+ = 260.26$.

Step 3 – Preparation of 5-iodo-4-methyl-7-triisopropylsilanyl-7H-pyrrolo[2,3-d]pyrimidine (20):

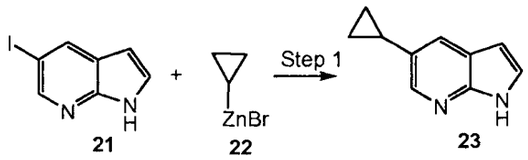
[0261] To 5-iodo-4-methyl-7H-pyrrolo[2,3-d]pyrimidine (**19**, 323.6 mg, 1.25 mmol) in 8 mL of tetrahydrofuran under nitrogen, sodium hydride (57.41 mg, 60% in mineral oil, 1.44 mmol) was added. The reaction was stirred at room temperature for 10 minutes, then triisopropysilyl chloride (**3**, 0.304 mL, 1.44 mmol) was added. The reaction was stirred at room temperature for 2 hours, then

poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound.

Example 8: Synthesis of 5-cyclopropyl-1H-pyrrolo[2,3-b]pyridine 23.

[0262] 5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridine **23** was prepared in one step from 5-iodo-1H-pyrrolo[2,3-b]pyridine **21** as shown in Scheme 8.

Scheme 8



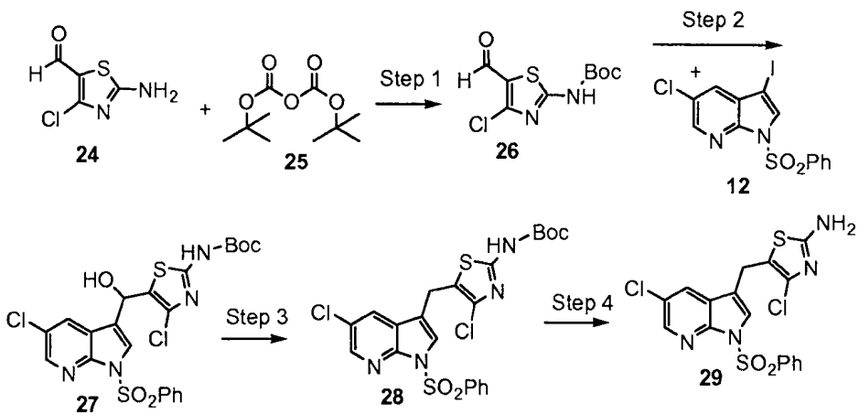
Step 1– Preparation of 5-cyclopropyl-1H-pyrrolo[2,3-b]pyridine (23):

[0263] 5-Iodo-1H-pyrrolo[2,3-b]pyridine (**21**, 0.343 g, 1.40 mmol), cyclopropylzinc bromide (**22**, 12.6 mL, 0.500 M in tetrahydrofuran, 6.32 mmol) and [1,3-bis(diphenylphosphino)propane]-nickel(II) chloride (76.2 mg, 0.14 mmol) and 5.37 mL of 1,4-dioxane were combined in a reaction vessel. The reaction was heated at 100 °C overnight, then methanol was added and the reaction was concentrated under vacuum. Ethyl acetate and water were added to the residue, then filtered through a bed of celite and the celite bed washed with ethyl acetate. The filtrate was separated and the aqueous layer extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate and hexane. Appropriate fraction were combined and concentrated under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+ = 159.0$.

Example 9: Synthesis of intermediate 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine 29

[0264] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **29** was synthesized in 4 steps from 2-amino-4-chloro-thiazole-5-carbaldehyde **24** as shown in Scheme 9.

Scheme 9



Step 1 – Synthesis of (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (26):

[0265] To 2-amino-4-chloro-thiazole-5-carbaldehyde (**24**, 5.00 g, 0.0308 mol) in 122 mL of tetrahydrofuran, di-tert-butyldicarbonate (**25**, 7.38 g, 0.0338 mol) and 4-dimethylaminopyridine (0.35 g, 0.0029 mol) were added. The reaction was stirred at 58 °C for 2 hours, then concentrated under vacuum and purified with silica gel column chromatography eluting with 20-80% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a yellow solid (**26**, 7.0 g, 87%).

Step 2 – Synthesis of 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-chloro-thiazol-2-yl-carbamic acid tert-butyl ester (27):

[0266] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**12**, 4.40 g, 10.5 mmol) in 30.0 mL of tetrahydrofuran at -45 °C under nitrogen, a solution of isopropylmagnesium chloride (5.4 mL, 2.0 M in tetrahydrofuran) was added slowly over 10 minutes. The reaction was allowed to warm to -25 °C over 30 minutes, then cooled to -65 °C, followed by adding the cold deprotonated (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester, which was prepared in situ by adding isopropylmagnesium chloride (5.0 mL, 2.0 M in tetrahydrofuran) to (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**26**, 2.51 g, 9.55 mmol) in 23.0 mL of tetrahydrofuran at -78 °C under nitrogen. The reaction was allowed to warm to room temperature over 2 hours, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 25-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**27**, 3.70 g, 60.3%). MS (ESI) $[M+H^+]^+ = 554.2$.

Step 3 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (28):

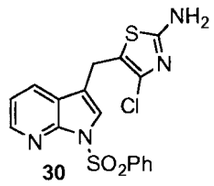
[0267] To 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-

chloro-thiazol-2-yl-carbamic acid tert-butyl ester (**27**, 0.200 g, 0.32 mmol) in 15.0 mL of dichloromethane, triethylsilane (0.600 mL, 376 mmol) and trifluoroacetic acid (0.300 mL, 3.89 mmol) were added. The reaction was stirred at room temperature for 3 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 25-100% ethyl acetate in hexane to give the desired compound (**28**, 0.155 g, 88.7%). MS (ESI) $[M+H^+]^+ = 538.9$.

*Step 4 – Synthesis of 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (**29**):*

[0268] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (**28**, 4.30 g, 7.97 mmol) in 70.0 mL of dichloromethane, a solution of hydrogen chloride (42.0 mL, 4.00 M in 1,4-dioxane) was added. The reaction was stirred at room temperature for 2 days, then concentrated, and triturated with ethyl ether and ethyl acetate to provide the desired compound (**29**, 2.60 g, 74.2%). MS (ESI) $[M+H^+]^+ = 439.0$.

[0269] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **30**



30

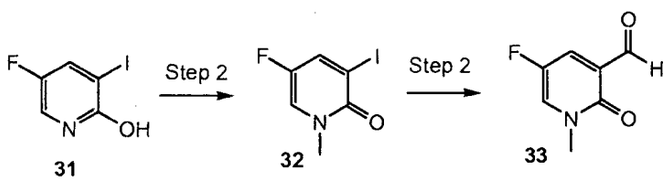
was prepared following the protocol of Scheme 9, substituting 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **12** with 1-benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine in Step 2. MS (ESI) $[M+H^+]^+ = 404.4$.

Example 10: Synthesis of aldehyde reagents.

[0270] Aldehyde reagents that are used in making compounds are prepared according to the following protocols.

[0271] 5-Fluoro-1-methyl-2-oxo-1,2-dihydro-pyridine-3-carbaldehyde **33** was prepared in two steps from 5-fluoro-3-iodo-pyridin-2-ol **31** as shown in Scheme 10a.

Scheme 10a



31 **32** **33**

Step 1 – Preparation of 5-fluoro-3-iodo-1-methyl-1H-pyridin-2-one (32):

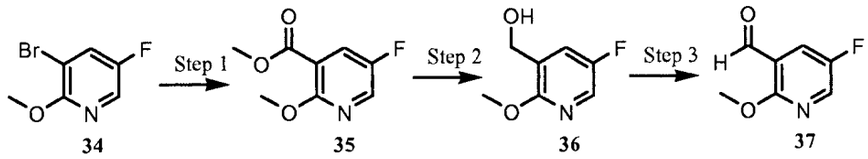
[0272] To 5-fluoro-3-iodo-pyridin-2-ol (**31**, 200 g, 838 mmol) in 3000 mL of acetone was cooled in an ice water bath. Cesium carbonate (354 g, 1088 mmol) was added, then iodomethane (58.1 mL, 929 mmol) was added dropwise over 30 minutes. The reaction was stirred overnight at room temperature. The reaction was concentrated under vacuum and the resulting material partitioned between ethyl acetate and water. The aqueous layer was isolated and adjusted to pH 3-4 with 3 N hydrochloric acid, then extracted with ethyl acetate. The combined organic layers were concentrated under vacuum to provide the desired compound as an off white solid. (**32**, 150 g, 593 mmol, 70.8%).

Step 2 – Preparation of 5-fluoro-1-methyl-2-oxo-1,2-dihydro-pyridine-3-carbaldehyde (33):

[0273] 5-Fluoro-3-iodo-1-methyl-1H-pyridin-2-one (**32**, 120.5 g, 476 mmol) was dissolved in 2381 mL of tetrahydrofuran and cooled to -40 °C in a dry ice acetone bath. Isopropylmagnesium chloride (310 mL, 619 mmol) was added dropwise and the mixture was stirred for 30 minutes. Then 92 mL of N,N-dimethylformamide was added and the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding 200 mL of 10% aqueous hydrochloric acid, then concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 100% ethyl acetate. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a yellow solid (**33**, 35 g, 226 mmol, 47.4%).

[0274] 5-Fluoro-2-methoxy-pyridine-3-carbaldehyde **37** was prepared in three steps from 3-bromo-5-fluoro-2-methoxy-pyridine **34** as shown in Scheme 10b.

Scheme 10b



Step 1 – Preparation of 5-fluoro-2-methoxy-nicotinic acid methyl ester (35):

[0275] In a 2L Parr bomb, 3-bromo-5-fluoro-2-methoxy-pyridine (**34**, 14 g, 68.0 mmol), triethylamine (19.10 mL, 136 mmol) and [1,1'-bis(diphenylposphino)ferrocene]-dichloropalladium(II) (1.443 g, 1.767 mmol) were combined with 300 mL of methanol and heated at 100 °C under 100 psi of carbon monoxide overnight. The reaction was concentrated under vacuum, the residue dissolved in dichloromethane, and passed through a plug of silica, eluting with ethyl acetate to provide the desired compound as a white solid (**35**, 10 g, 54.0 mmol, 79%).

Step 2 – Preparation of (5-fluoro-2-methoxy-pyridin-3-yl)-methanol (36):

[0276] To 5-fluoro-2-methoxy-nicotinic acid methyl ester (**35**, 10 g, 54.0 mmol) in 200 mL of

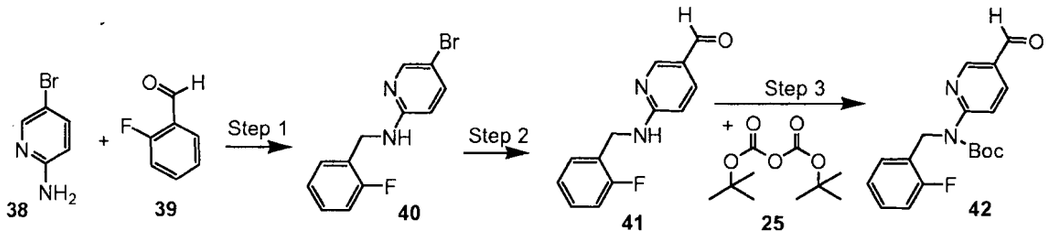
tetrahydrofuran, lithium aluminum hydride (81 mL, 1 M in tetrahydrofuran, 81 mmol) was added dropwise at -78 °C and stirred for several hours. The reaction was quenched with dropwise addition of 3 mL water, 3 mL of 15% aquous sodium hydroxide, and 10 mL of water sequentially, then 200 mL of methyl t-butyl ether was added. Solids were filtered out and the filtrate concentrated under vacuum to provide the desired compound as a white solid (**36**, 8 g, 50.9 mmol, 94%).

Step 3 – Preparation of 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (37):

[0277] To (5-fluoro-2-methoxy-pyridin-3-yl)-methanol (**36**, 8 g, 50.9 mmol) in 300 mL of ethyl acetate, manganese(IV) oxide (39.8 g, 458 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was filtered through celite, and the celite bed rinsed with ethyl acetate. The filtrate was concentrated under vacuum, then passed through a plug of silica, eluting with 50% ethyl acetate in heptane to provide the desired compound as a light yellow solid (**37**, 4.5 g, 29.0 mmol, 57.0% yield).

[0278] (2-Fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **42** was prepared in three steps from 5-bromo-pyridin-2-ylamine **38** and 2-fluoro-benzaldehyde **39** as shown in Scheme 10c.

Scheme 10c



Step 1 – Preparation of (5-bromo-pyridin-2-yl)-(2-fluoro-benzyl)-amine (40):

[0279] In a round bottom flask, 5-bromo-pyridin-2-ylamine (**38**, 4.05 g g, 23.4 mmol) was combined with 70.0 mL of acetonitrile, 2-fluoro-benzaldehyde (**39**, 2.45 mL, 23.4 mmol), triethylsilane (20.0 mL, 125 mmol) and trifluoroacetic acid (10.0 mL, 130 mmol). The reaction was stirred at 80 °C for 3 hours. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-60% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound (**40**, 5.0g).

Step 2 – Preparation of 6-(2-fluoro-benzylamino)-pyridine-3-carbaldehyde (41):

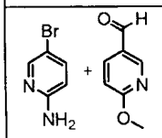
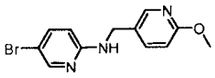
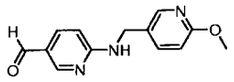
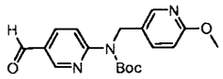
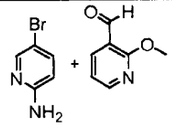
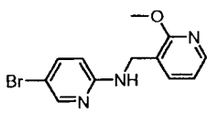
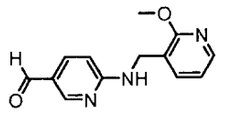
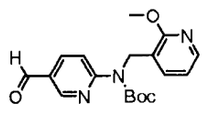
[0280] In a round bottom flask, (5-bromo-pyridin-2-yl)-(2-fluoro-benzyl)-amine (**40**, 3.90 g, 13.9 mmol) was combined with 60.0 mL of tetrahydrofuran at -78 °C under nitrogen and tert-butyllithium (5.57 mL, 2.50 M in hexane) was added over 5 minutes. After 30 minutes additional tert-butyllithium

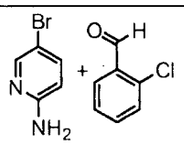
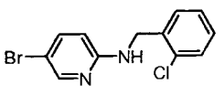
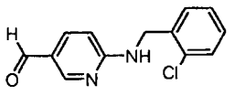
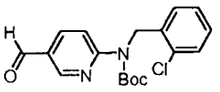
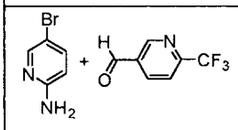
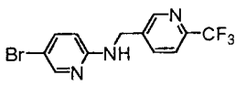
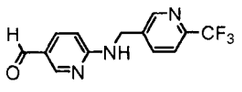
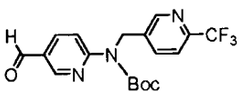
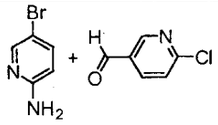
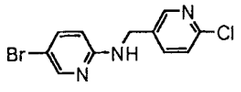
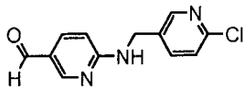
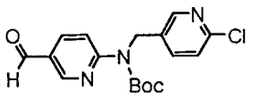
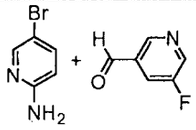
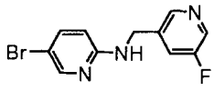
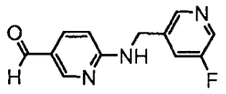
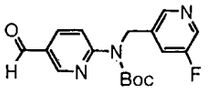
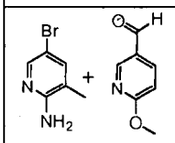
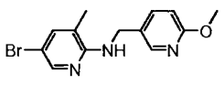
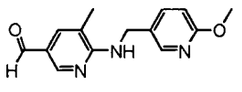
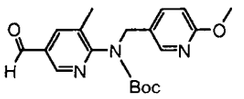
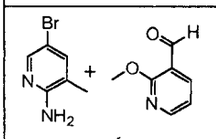
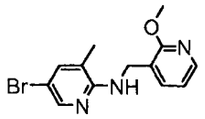
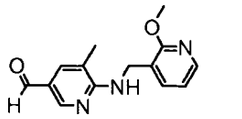
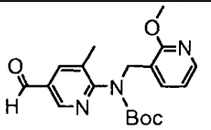
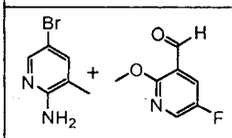
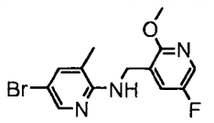
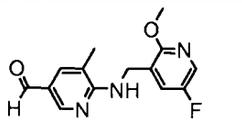
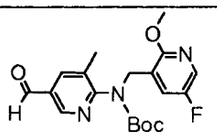
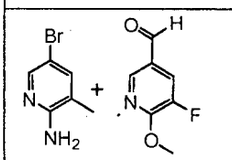
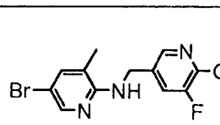
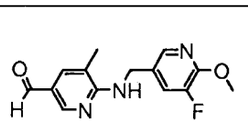
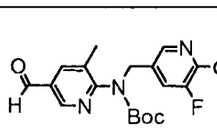
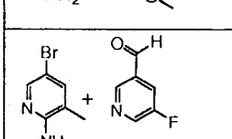
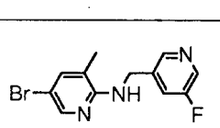
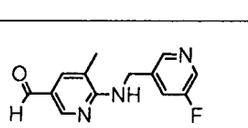
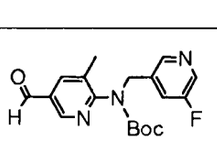
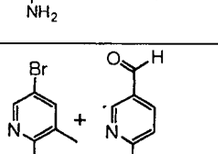
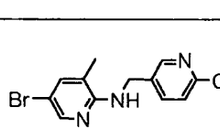
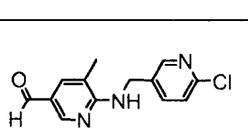
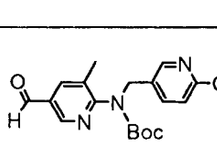
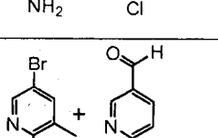
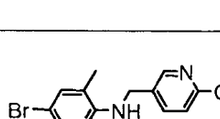
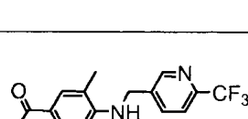
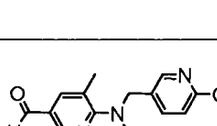
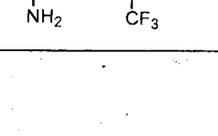
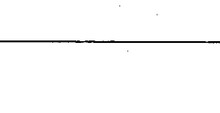
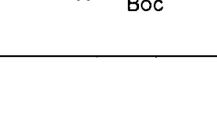
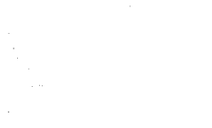
(17.1 mL, 1.7 M in hexane) was added over 5 minutes. After 25 minutes, N,N-dimethylformamide (2.6 mL, 34 mmol) was added and the mixture was stirred for 70 minutes at -78 °C, then allowed to warm up to room temperature for 1 hour. The reaction was poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic portion was dried with sodium sulfate, filtered and filtrate concentrated under vacuum to provide the desired compound (**41**, 3.0 g), which was used in the next step without further purification.

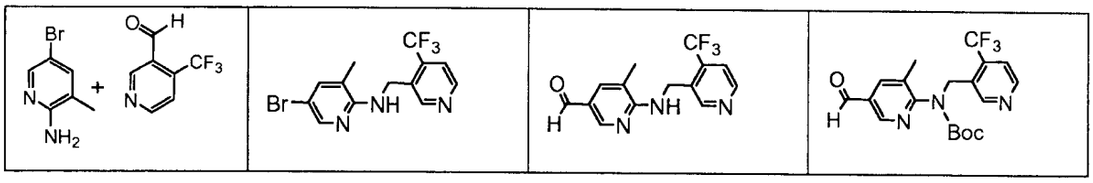
Step 3 – Preparation of (2-fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (42):

[0281] To 6-(2-fluoro-benzylamino)-pyridine-3-carbaldehyde (**41**, 3.00 g, 13.0 mmol) in 57.2 mL of tetrahydrofuran, di-tert-butyldicarbonate (**25**, 4.26 g, 19.5 mmol) and 4-dimethylaminopyridine (0.16 g, 1.3 mmol) and triethylamine (3.6 mL, 26 mmol) were added. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic portion was dried with sodium sulfate, filtered and filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to give the desired compound (**41**, 3.50 g).

[0282] Additional aldehydes are prepared similarly to the protocol of Scheme 10c, as shown in the following table, where Step 1, Step 2 and Step 3 reactants are provided in columns 1, 2, and 3, respectively, with the resulting Boc protected aldehyde provided in column 4. Reaction conditions are similar to those described for Scheme 10c, and may vary slightly for each step, for example, any of the solvents, reagents, reaction times, 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. For example, without limitation, for step 2, the first addition of t-butyllitium is replaced with n-butyllithium in pentane or by isopropylmagnesium chloride in tetrahydrofuran; for step 3, triethylamine is replaced with N,N-diisopropylethylamine, or dichloromethane is used as solvent. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

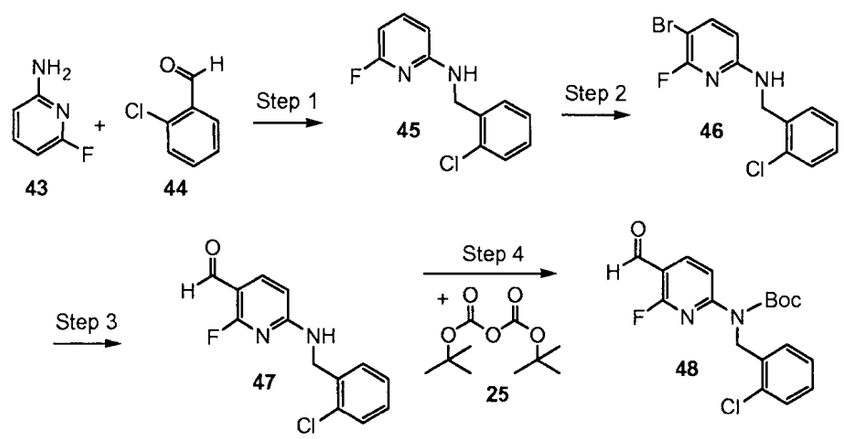
Step 1	Step 2	Step 3	Final aldehyde
			
			



[0283] (2-Chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **48** was prepared in four steps from 6-fluoro-pyridin-2-ylamine **43** and 2-chloro-benzaldehyde **44** as shown in Scheme 10d.

Scheme 10d



Step 1 – Preparation of (2-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (45):

[0284] To 6-fluoro-pyridin-2-ylamine (**43**, 2.47 g, 22.0 mmol) in 60.0 mL of acetonitrile, 2-chloro-benzaldehyde (**44**, 3.09 g, 22.0 mmol), triethylsilane (14.0 mL, 87.6 mmol) and trifluoroacetic acid (7.00 mL, 90.9 mmol) were added. The reaction was stirred at 80 °C for 4 hours, then solvents removed under vacuum, and the residue was combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound, which was used in the next step without further purification. MS (ESI) $[M+H^+]^+ = 272.1$.

Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine (46):

[0285] To (2-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (**45**, 4.70 g, 19.8 mmol) in 100.0 mL of acetonitrile, N-bromosuccinimide (3.53 g, 19.8 mmol) in 20.0 mL of acetonitrile was added slowly at room temperature. The reaction was stirred at room temperature for 4 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was washed with ethyl acetate in hexane to provide the desired compound (**46**, 5.0 g).

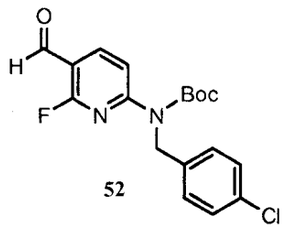
Step 3 – Preparation of 6-(2-chloro-benzylamino)-2-fluoro-pyridine-3-carbaldehyde (47):

[0286] To (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine (**46**, 1.85 g, 5.86 mmol) in 25.0 mL of tetrahydrofuran under nitrogen at -78 °C, isopropylmagnesium chloride (3.00 mL, 2.00 M in tetrahydrofuran, 6.00 mmol) was added over 10 minutes. After 50 minutes, tert-butyllithium (7.80 mL, 1.70 M in hexane, 13.3 mmol) was added over 5 minutes. After 20 minutes, N,N-dimethylformamide (1.09 mL, 14.0 mmol) was added and the reaction mixture stirred at -78 °C for 20 minutes, then brought to room temperature over 30 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 35% ethyl acetate in hexane. The appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound (**47**, 1.45 g). MS (ESI) $[M+H^+]^+ = 265.4$.

Step 4 – Preparation of (2-chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (48):

[0287] To 6-(2-chloro-benzylamino)-2-fluoro-pyridine-3-carbaldehyde (**47**, 1.45 g, 5.48 mmol) in 31.4 mL of tetrahydrofuran, di-tert-butyldicarbonate (**25**, 1.79 g, 8.22 mmol) and 4-dimethylaminopyridine (78.6 mg, 0.643 mmol) were added. The reaction was stirred at room temperature for 3 hours, then concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 15-35% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound as a colorless oil (**48**, 1.60 g).

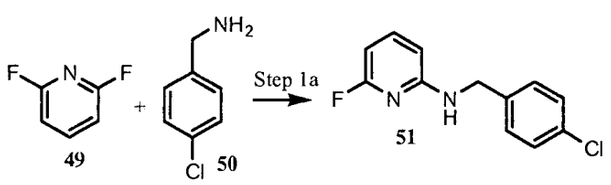
[0288] (4-Chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **52**



52

was prepared similarly to the protocol of Scheme 10d, with the first step modified by reacting 2,6-difluoro-pyridine **49** and 4-chloro-benzylamine **50** according the following step 1a.

Scheme 10d Step 1a

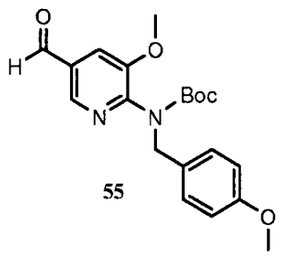


49 **50** **51**

Step 1 – Preparation of (4-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (51):

[0289] To 2,6-difluoro-pyridine (**49**, 3.80 g, 33.0 mmol) in 20.0 mL of N-methylpyrrolidone, 4-chloro-benzylamine (**50**, 5.6 mL, 46.0 mmol) and N,N-diisopropylethylamine (10.0 mL, 57.4 mmol) were added. The reaction was stirred at 90 °C overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 25% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum, and the resulting material was washed with ethyl acetate/hexane to provide the desired compound as a white solid (**51**, 5.30 g).

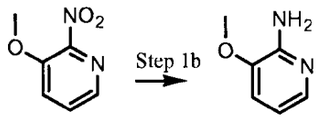
[0290] 3-methoxy-pyridin-2-ylamine **54**, for use in step 1 of Scheme 10d in the preparation of (5-formyl-3-methoxy-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **55**



55

was prepared in one step from 3-methoxy-2-nitro-pyridine **53** by the following step 1b.

Scheme 10d Step 1b



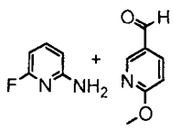
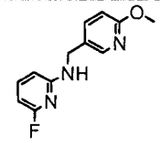
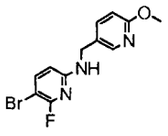
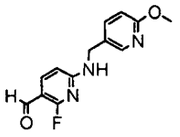
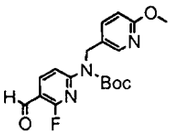
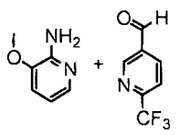
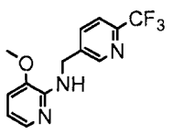
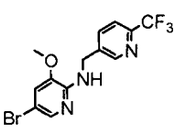
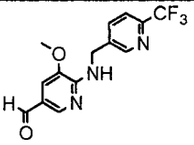
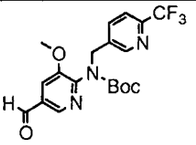
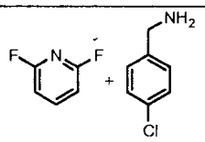
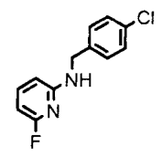
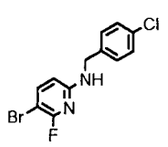
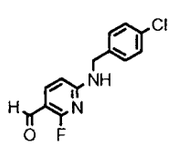
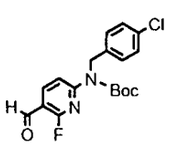
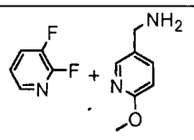
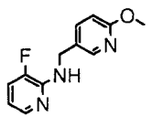
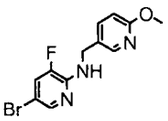
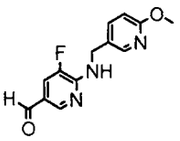
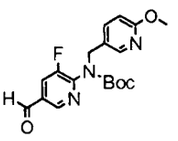
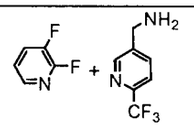
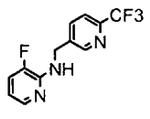
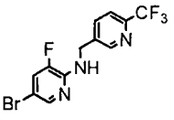
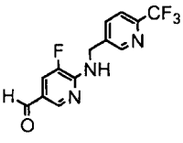
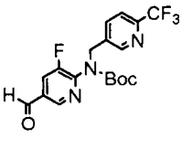
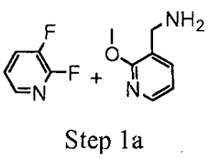
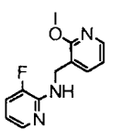
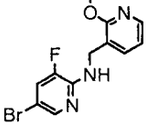
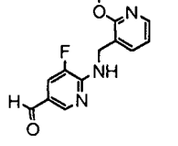
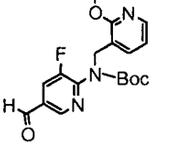
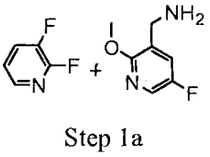
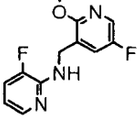
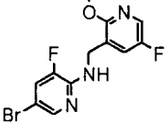
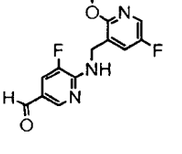
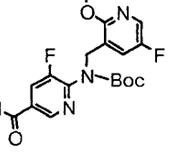
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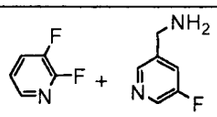
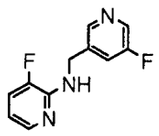
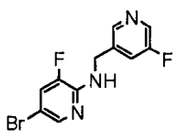
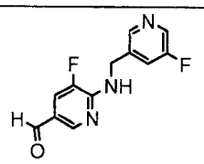
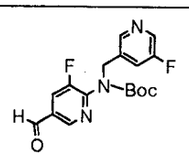
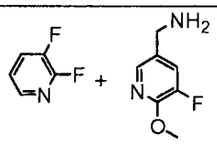
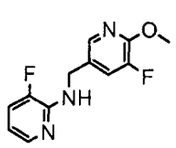
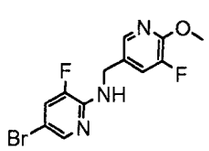
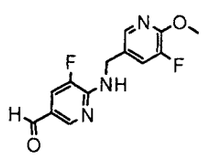
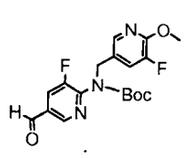
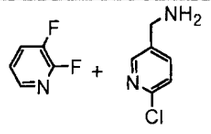
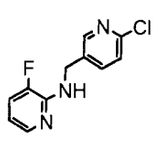
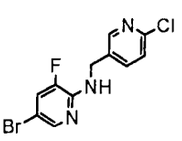
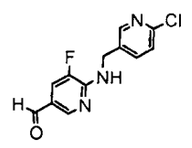
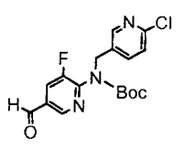
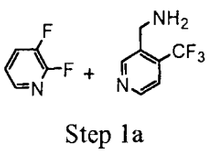
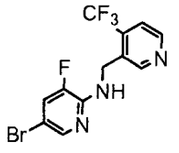
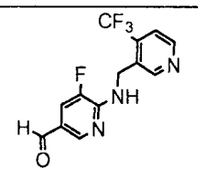
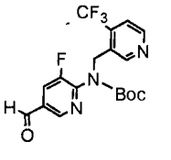
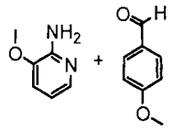
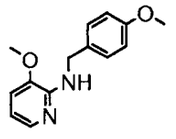
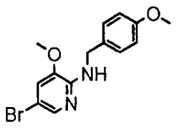
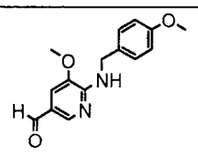
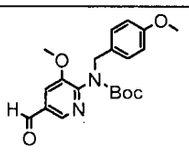
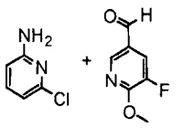
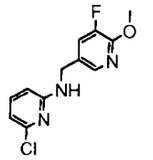
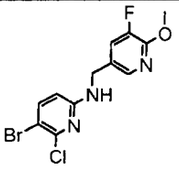
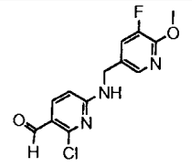
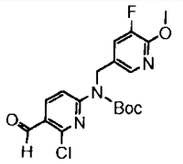
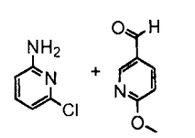
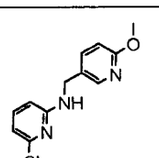
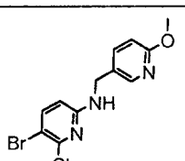
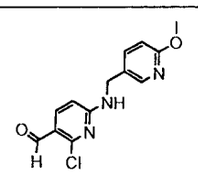
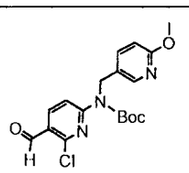
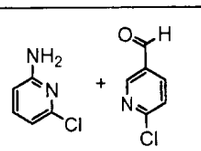
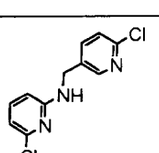
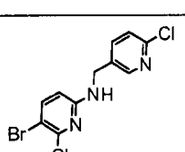
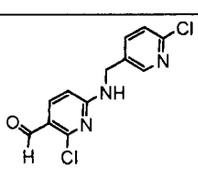
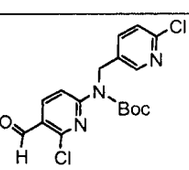
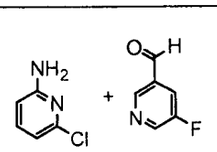
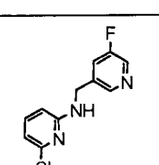
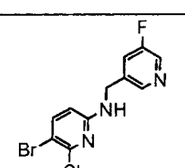
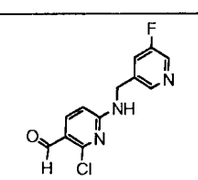
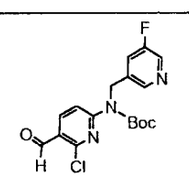
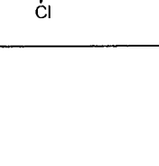
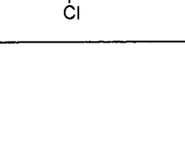
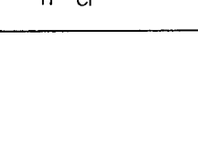
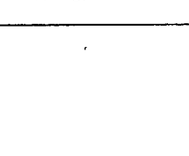
Step 1 – Preparation of 3-methoxy-pyridin-2-ylamine (54):

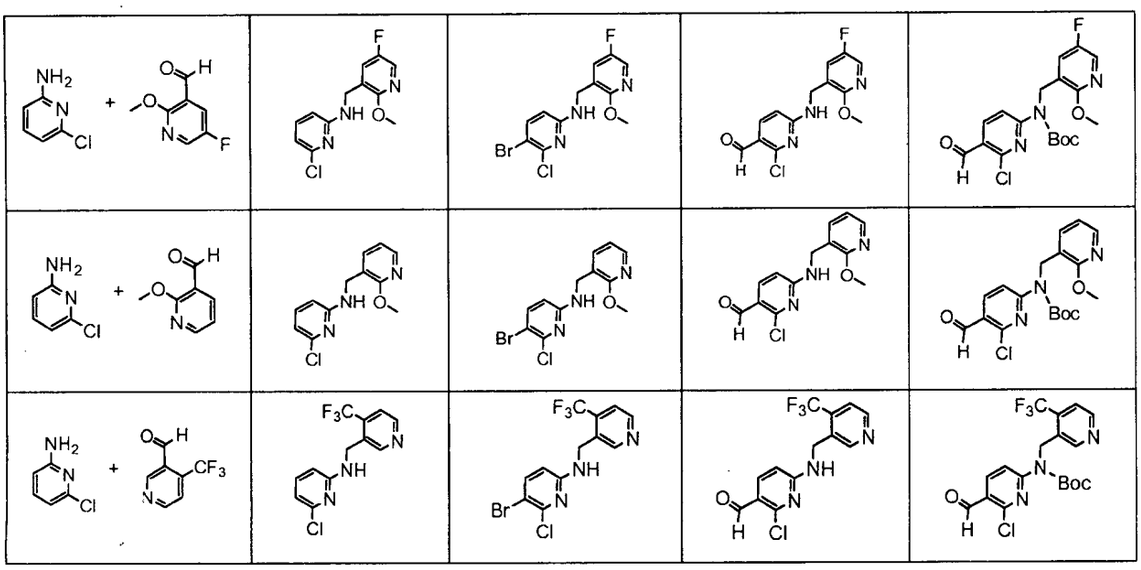
[0291] 3-Methoxy-2-nitro-pyridine (**53**, 7.00 g, 45.4 mmol) in 100 mL of methanol, was degassed and palladium (0.7 g, 20%) was added. The reaction was stirred at room temperature for one day under a hydrogen balloon. The reaction was filtered through celite and the filtrate concentrated under vacuum to provide the desired compound (**54**, 5.555 g). MS (ESI) $[M+H^+]^+ = 125.3$.

[0292] Additional aldehydes are prepared similarly to the protocol of Scheme 10d, as shown in the following table, where Step 1 (or 1a), Step 2, Step 3 and Step 4 reactants are provided in columns 1, 2, 3, and 4, respectively, with the resulting Boc protected aldehyde provided in column 5. Step 1a use is indicated in column 1. Reaction conditions are similar to those described for Scheme 10d, and may vary slightly for each step, for example, any of the solvents, reagents, reaction times, 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

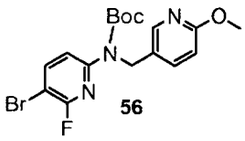
skilled in the art. For example, without limitation, for step 1a, no N,N-diisopropylethylamine is used; for step 3, the addition of isopropylmagnesium chloride is replaced with n-butyllithium in hexane; for step 4, triethylamine is included in the reaction and dichloromethane is used as solvent. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

Step 1	Step 2	Step 3	Step 4	Final aldehyde
				
				
 Step 1a				
 Step 1a				
 Step 1a				
 Step 1a				
 Step 1a				

 Step 1a				
 Step 1a				
 Step 1a				
 Step 1a				
				
				
				
				
				
				



[0293] (5-Bromo-6-fluoro-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **56**

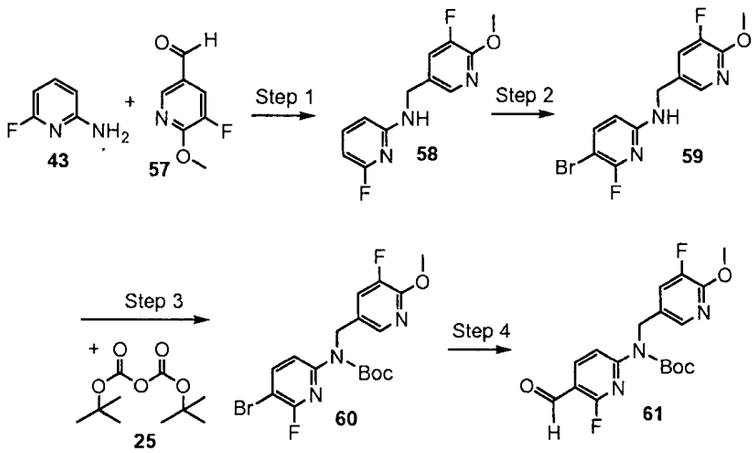


56

was prepared from the product of step 2 for the first entry of the table, which was then Boc protected similarly to the protocol of Scheme 10d step 4.

[0294] (6-Fluoro-5-formyl-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **61** was prepared in four steps from 6-fluoro-pyridin-2-ylamine **43** and 5-fluoro-6-methoxy-pyridine-3-carbaldehyde **57** as shown in Scheme 10e.

Scheme 10e



*Step 1 – Preparation of (5-fluoro-6-methoxy-pyridin-3-ylmethyl)-(6-fluoro-pyridin-2-yl)-amine (**58**):*

[0295] To 6-fluoro-pyridin-2ylamine (**43**, 1.50 g, 13.4 mmol) in 52.9 mL of acetonitrile, 5-fluoro-6-methoxy-pyridine-3-carbaldehyde (**57**, 2.00 g, 12.9 mmol), triethylsilane (10.6 mL, 66.3 mmol), and trifluoroacetic acid (5.3 mL, 69.0 mmol) were added. The reaction was stirred at 80 °C overnight, then concentrated under vacuum, combined with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 15-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as white solid (**58**, 3.21 g).

*Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**59**):*

[0296] To (5-fluoro-6-methoxy-pyridin-3-ylmethyl)-(6-fluoro-pyridin-2-yl)-amine (**58**, 3.21 g, 12.8 mmol) in 100 mL of acetonitrile, N-bromosuccinimide (2.30 g, 12.9 mmol) in 30 mL of acetonitrile was added slowly at room temperature. The reaction was stirred at room temperature for 4 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**59**, 3.60 g).

*Step 3 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**60**):*

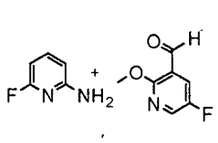
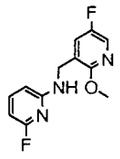
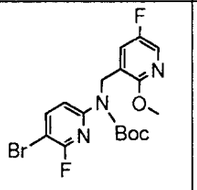
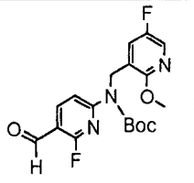
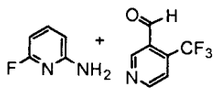
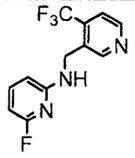
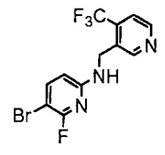
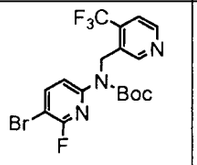
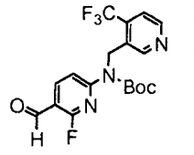
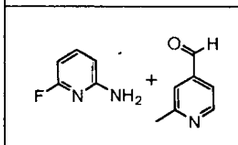
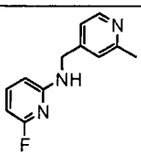
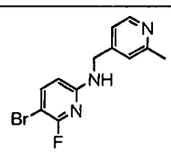
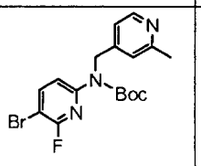
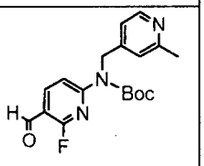
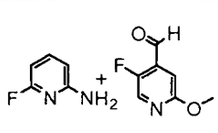
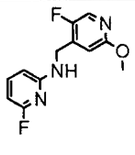
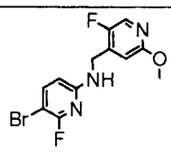
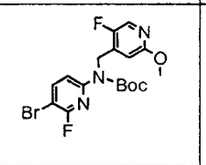
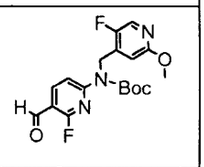
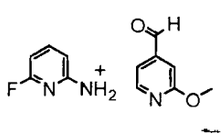
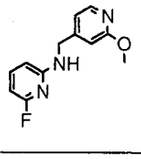
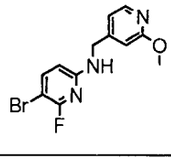
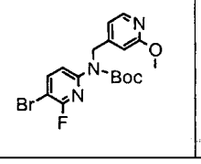
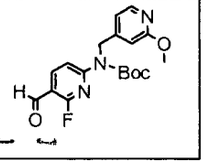
[0297] To (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**59**, 2.70 g, 8.18 mmol) in 58.7 mL of tetrahydrofuran, di-tert-butyldicarbonate (**25**, 2.2 g, 9.9 mmol) and 4-dimethylaminopyridine (0.29 g, 2.4 mmol) were added. The reaction was stirred at room temperature for 90 minutes, then concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a colorless oil (**60**, 3.0 g).

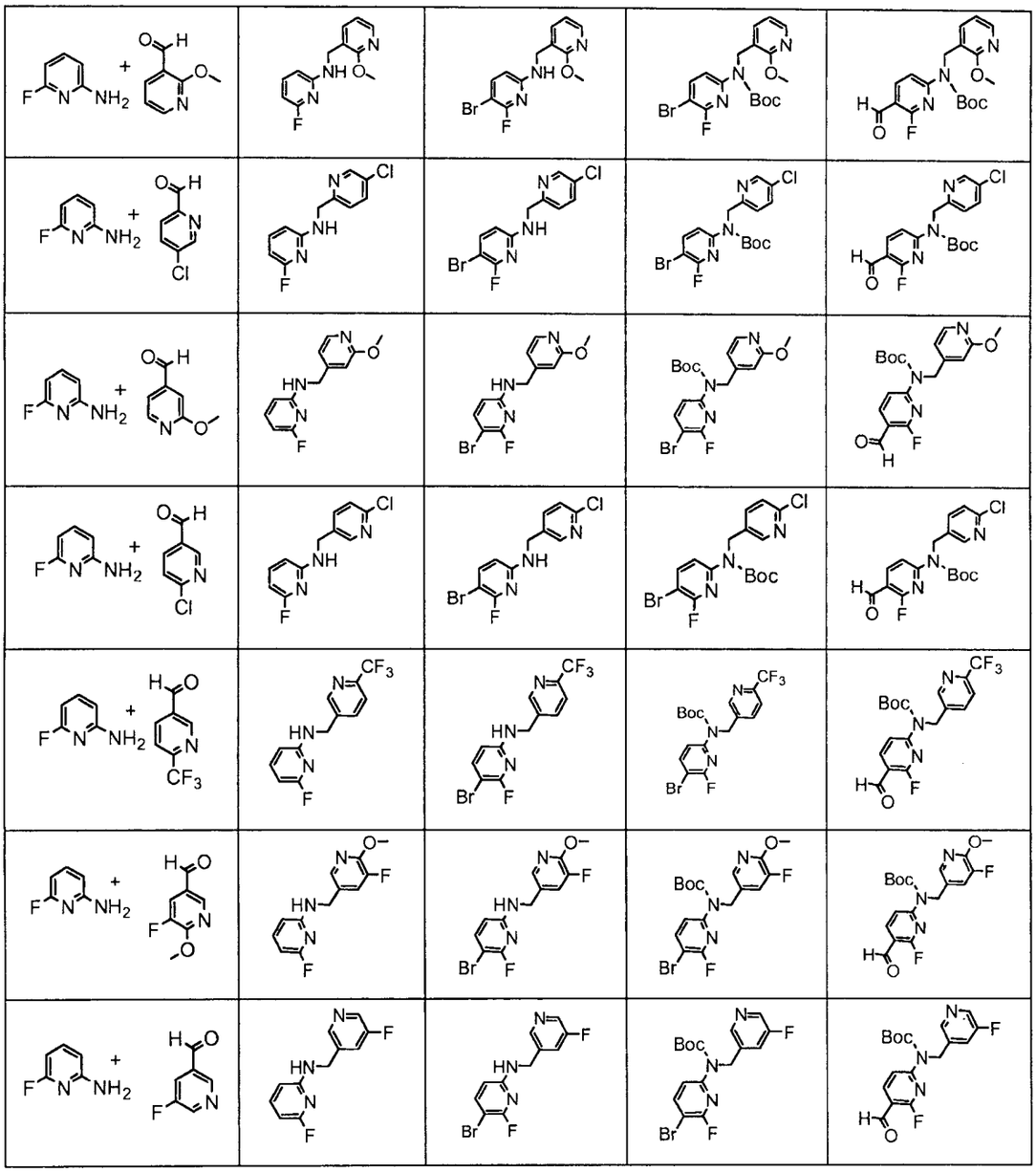
*Step 4 – Preparation of (6-fluoro-5-formyl-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**61**):*

[0298] To (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**60**, 2.90 g, 6.74 mmol) in 25.0 mL of tetrahydrofuran at -35 °C under nitrogen, isopropylmagnesium chloride (3.54 mL, 2.00 M in tetrahydrofuran, 7.08 mmol) was added and the reaction was allowed to come to 0 °C over an hour. The reaction was cooled to -45 °C and N,N-dimethylformamide (1.0 mL, 13.0 mmol) was added. The reaction was allowed to warm to room

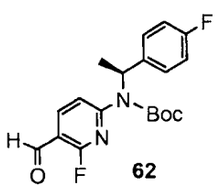
temperature over 2 hours, then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**61**, 1.80 g).

[0299] Additional aldehydes are prepared similarly to the protocol of Scheme 10e, as shown in the following table, where Step 1, Step 2, Step 3 and Step 4 reactants are provided in columns 1, 2, 3, and 4, respectively, with the resulting Boc protected aldehyde provided in column 5. In some instances, the desired compound is the Boc proteced bromo compound isolated after step 3 for use in subsequent reactions. Reaction conditions are similar to those described for Scheme 10e, and may vary slightly for each step, for example, any of the solvents, reagents, reaction times, 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. For example, without limitation, step 2 is performed under nitrogen; step 3 includes N,N-diisopropylethylamine. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

Step 1	Step 2	Step 3	Step 4	Final aldehyde
				
				
				
				
				



[0300] (6-Fluoro-5-formyl-pyridin-2-yl)-[(S)-1-(4-fluoro-phenyl)-ethyl]-carbamic acid tert-butyl ester **62**

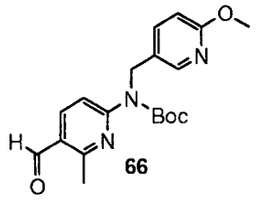


62

was prepared from 2,6-difluoro-pyridine **49** and (S)-1-(4-fluoro-phenyl)-ethylamine similarly to the protocol of step 1a of Scheme 10d, then steps 2-4 of Scheme 10c. Step 3 also included N,N-

diisopropylethylamine, as well as a subsequent addition of di-tert-butyldicarbonate and N,N-diisopropylethylamine.

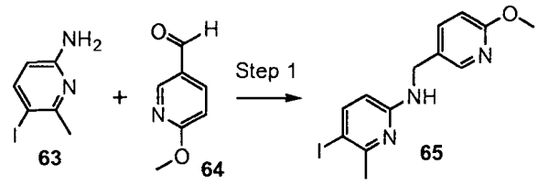
[0301] (5-Formyl-6-methyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **66**



66

was prepared by reacting (5-iodo-6-methyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-amine **65** similarly to the protocol of Scheme 10c, steps 3 and 4, where step 3 included N,N-diisopropylethylamine. (5-Iodo-6-methyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-amine **65** was prepared in one step from 5-iodo-6-methyl-pyridin-2-ylamine **63** and 6-methoxy-pyridine-3-carbaldehyde **64** as shown in Scheme 10f.

Scheme 10f



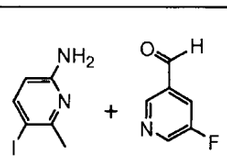
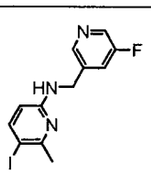
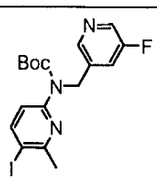
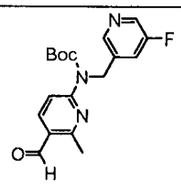
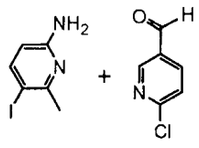
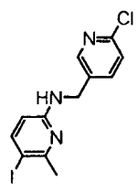
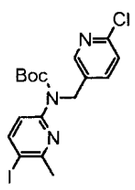
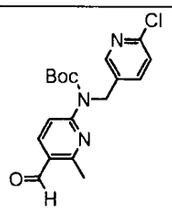
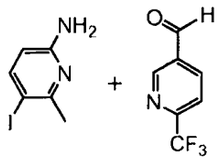
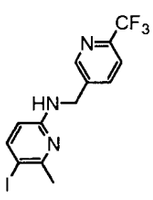
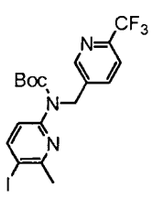
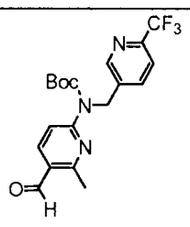
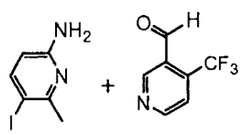
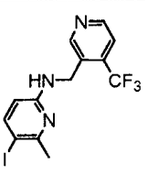
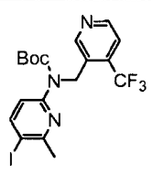
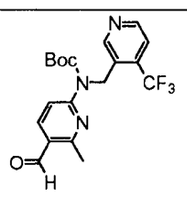
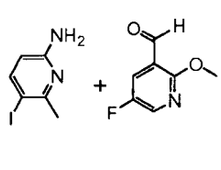
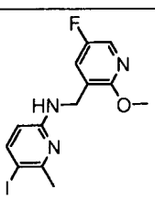
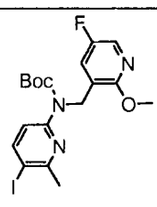
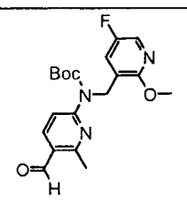
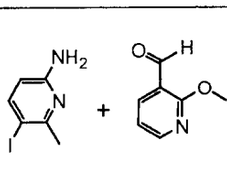
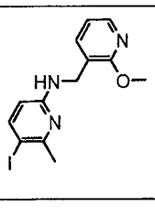
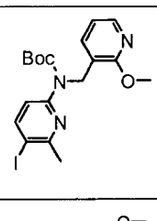
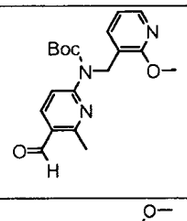
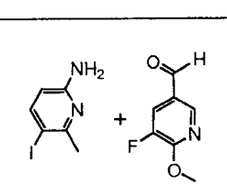
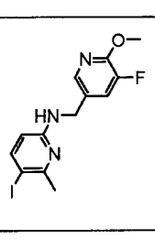
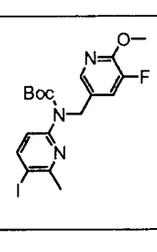
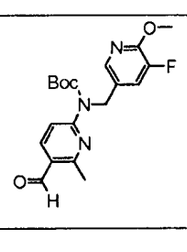
63 **64** **65**

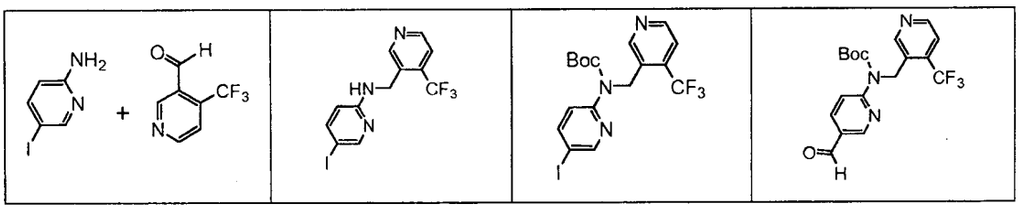
Step 1 – Preparation of (5-iodo-6-methyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-amine (65):

[0302] 5-Iodo-6-methyl-pyridin-2-ylamine (**63**, 1.7 g, 7.3 mmol) and 6-methoxy-pyridine-3-carbaldehyde (**64**, 1.1 g, 8.0 mmol) were combined in a round bottom flask with trifluoroacetic acid (2.80 mL, 36.3 mmol), triethylsilane (5.80 mL, 36.3 mmol) and 50 mL of acetonitrile. The reaction was stirred at room temperature overnight, then heated to reflux for 6 hours. The reaction was concentrated under vacuum, combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel flash column chromatography, eluting with 10-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**65**, 1.80 g). MS (ESI)$[M+H^+]^+ = 356.80$.

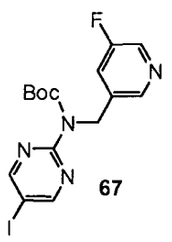
[0303] Additional aldehydes are prepared similarly to the protocol of Scheme 10f followed by Scheme 10e steps 2 and 3, as shown in the following table, where Step 1 (Scheme 10f), Step 3 and Step 4 reactants are provided in columns 1, 2, and 3, respectively, with the resulting Boc protected aldehyde provided in column 5. Reaction conditions are similar to those described for Schemes 10e and 10f, and may vary slightly for each step, for example, any of the solvents, reagents, reaction

times, 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.

Step 1	Step 3	Step 4	Final aldehyde
			
			
			
			
			
			
			
			



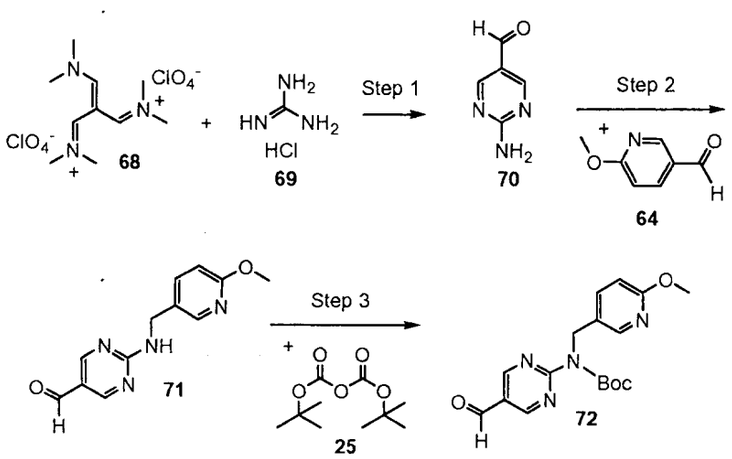
[0304] (5-fluoro-pyridin-3-ylmethyl)-(5-iodo-pyrimidin-2-yl)-carbamic acid tert-butyl ester **67**



was prepared similarly to Scheme 10f, replacing 5-iodo-6-methyl-pyridin-2-ylamine **63** with 5-iodo-pyrimidin-2-ylamine and 6-methoxy-pyridine-3-carbaldehyde **64** with 5-fluoro-pyridine-3-carbaldehyde and Boc-protecting the nitrogen, for example following similar protocol to Scheme 10e, step 3.

[0305] (5-Formyl-pyrimidin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **72** was prepared in three steps from vinamidinium salt **68** and guanidine hydrochloride **69** as shown in Scheme 10g.

Scheme 10g



Step 2 – Preparation of 2-amino-pyrimidine-5-carbaldehyde (70):

[0306] Vinamidinium salt (**68**, 158 g, 413 mmol) and guanidine hydrochloride (**69**, 63.3 g, 455 mmol) were dissolved in 527 mL of acetonitrile and cooled on an ice/water bath. Sodium hydroxide

(66.1 mL, 50% w/w, 827 mmol) was added dropwise, keeping the temperature below 25 °C. The reaction was allowed to warm to 25 °C and stirred for 4 hours, then diluted with water and filtered, stripped from ethanol/heptane, then triturated with heptane. The resulting solid was dried under vacuum to provide the desired compound (**70**, 37 g, 301 mmol, 72.7% yield).

Step 2 – Preparation of 2-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbaldehyde (71):

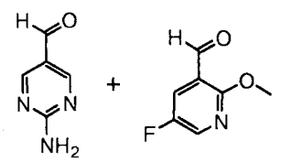
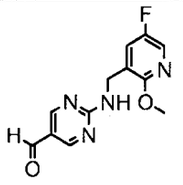
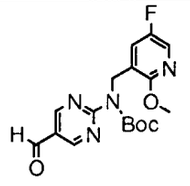
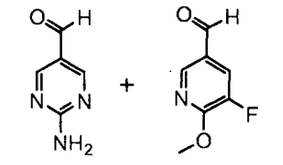
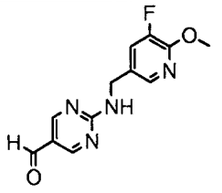
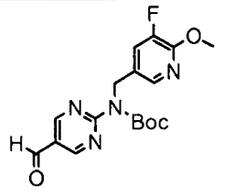
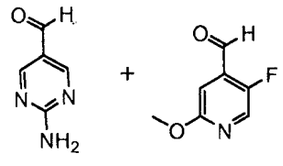
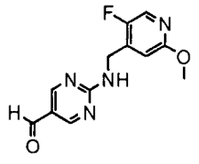
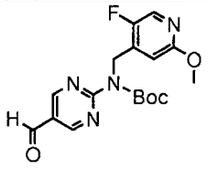
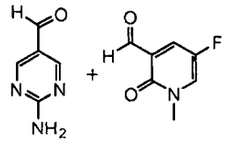
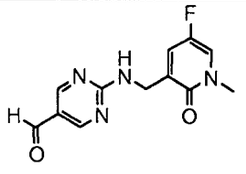
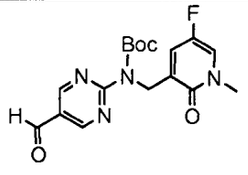
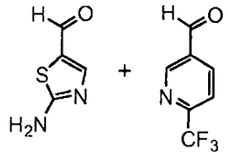
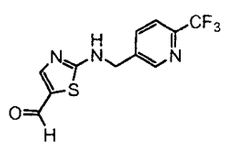
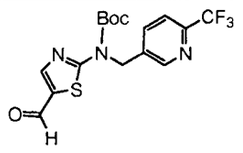
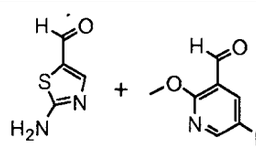
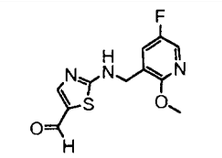
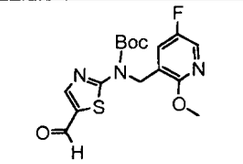
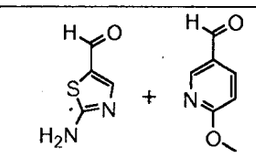
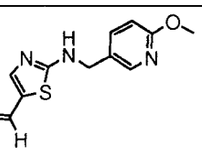
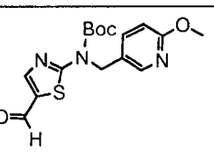
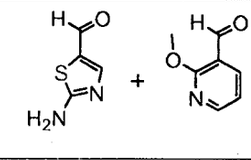
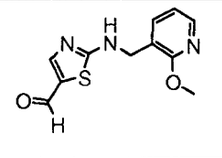
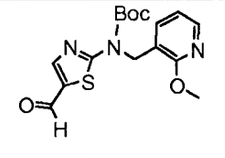
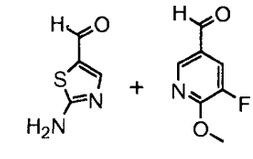
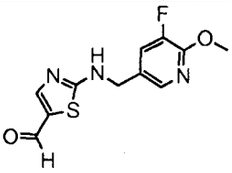
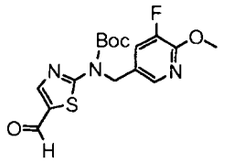
[0307] In a round bottom flask, 2-amino-pyrimidine-5-carbaldehyde (**70**, 0.750 g, 6.09 mmol), 6-methoxy-pyridine-3-carbaldehyde (**64**, 1.67 g, 12.2 mmol), trifluoroacetic acid (2.5 mL, 32.0 mmol), and triethylsilane (5.00 mL, 31.3 mmol) were combined with 10 mL of acetonitrile. The reaction was stirred at room temperature overnight, then concentrated under vacuum and combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel flash column chromatography, eluting with 15-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound.

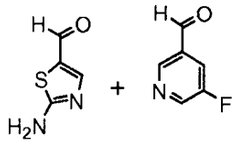
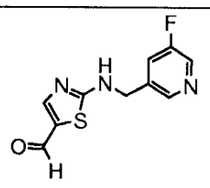
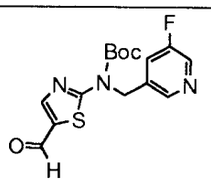
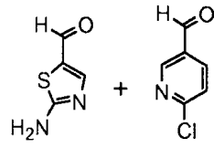
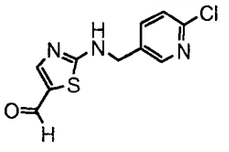
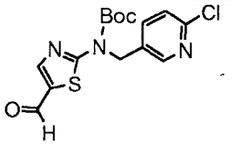
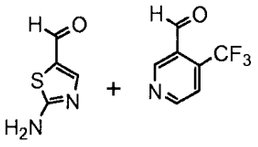
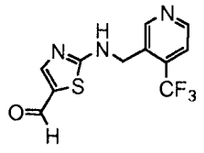
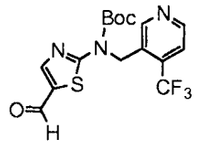
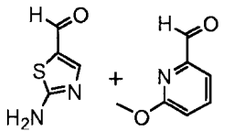
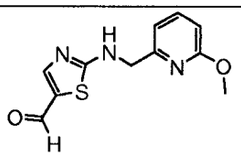
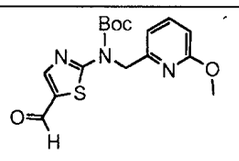
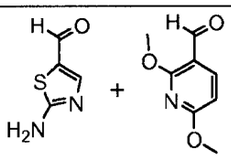
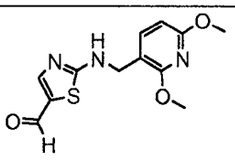
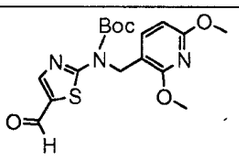
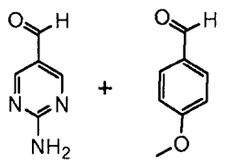
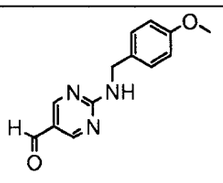
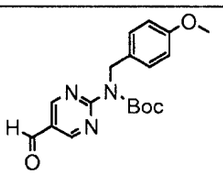
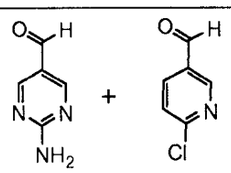
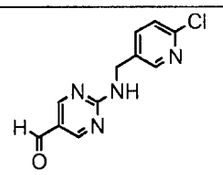
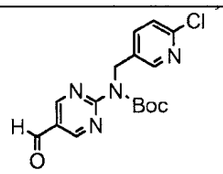
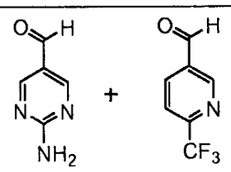
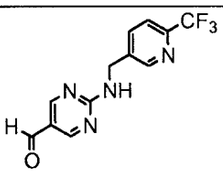
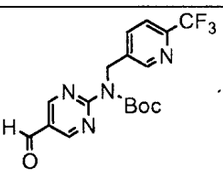
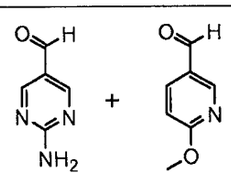
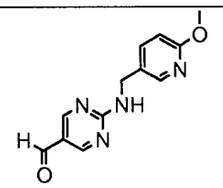
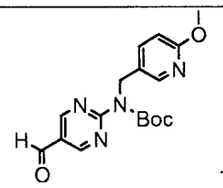
Step 3 – Preparation of (5-formyl-pyrimidin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (72):

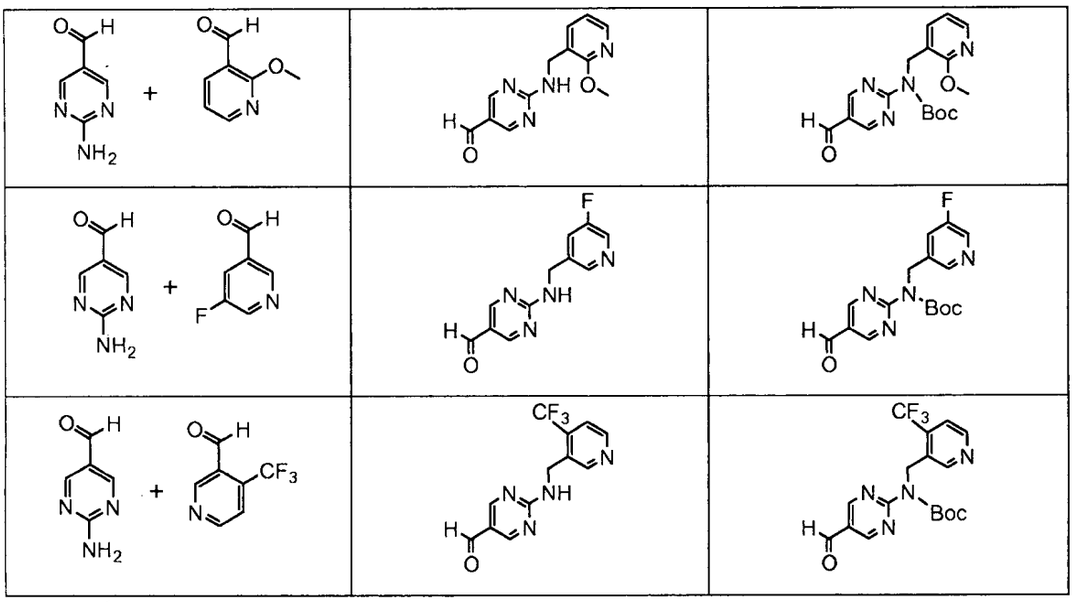
[0308] To 2-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbaldehyde (**71**, 0.462 g, 1.89 mmol) in 15 mL of tetrahydrofuran, N,N-diisopropylethylamine (0.72 mL, 4.2 mmol), 4-dimethylaminopyridine (0.02 g, 0.2 mmol) and di-tert-butyldicarbonate (**25**, 0.45 g, 2.1 mmol) were added. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was concentrated under vacuum and the resulting material was purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound. ^{1}H NMR was consistent with the compound structure.

[0309] Additional aldehydes are prepared similarly to the protocol of Scheme 10g, as shown in the following table, where Step 1 and Step 2 reactants are provided in columns 1 and 2, respectively, with the resulting Boc protected aldehyde provided in column 3. Reaction conditions are similar to those described for Scheme 10g, and may vary slightly for each step, for example, any of the solvents, reagents, reaction times, 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. For example, without limitation, for step 2, N,N-diisopropylethylamine is not included in the reaction. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

Step 1	Step 2	Final aldehyde

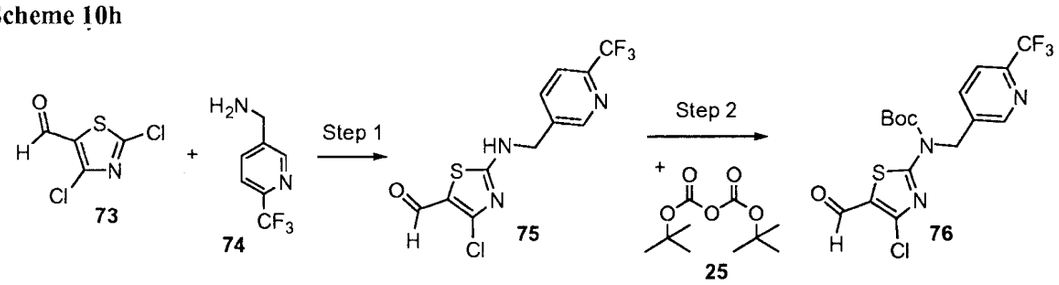
		
		
		
		
		
		
		
		
		



[0310] (4-Chloro-5-formyl-thiazol-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **76** was prepared in two steps from 2,4-dichloro-thiazole-5-carbaldehyde **73** and C-(6-trifluoromethyl-pyridin-3-yl)-methylamine **74** as shown in Scheme 10h.

Scheme 10h



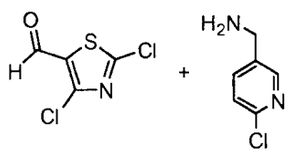
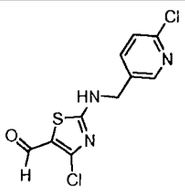
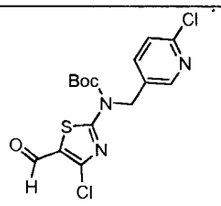
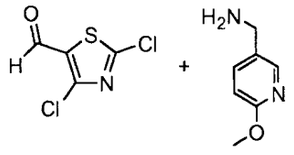
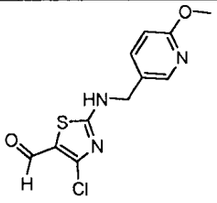
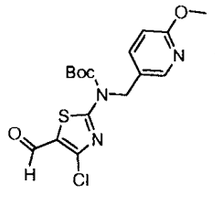
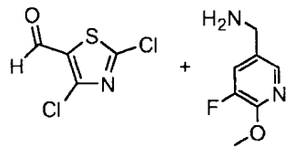
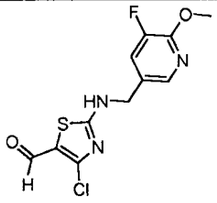
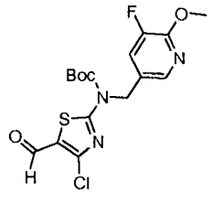
Step 1 – Preparation of 4-chloro-2-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-thiazole-5-carbaldehyde (75):

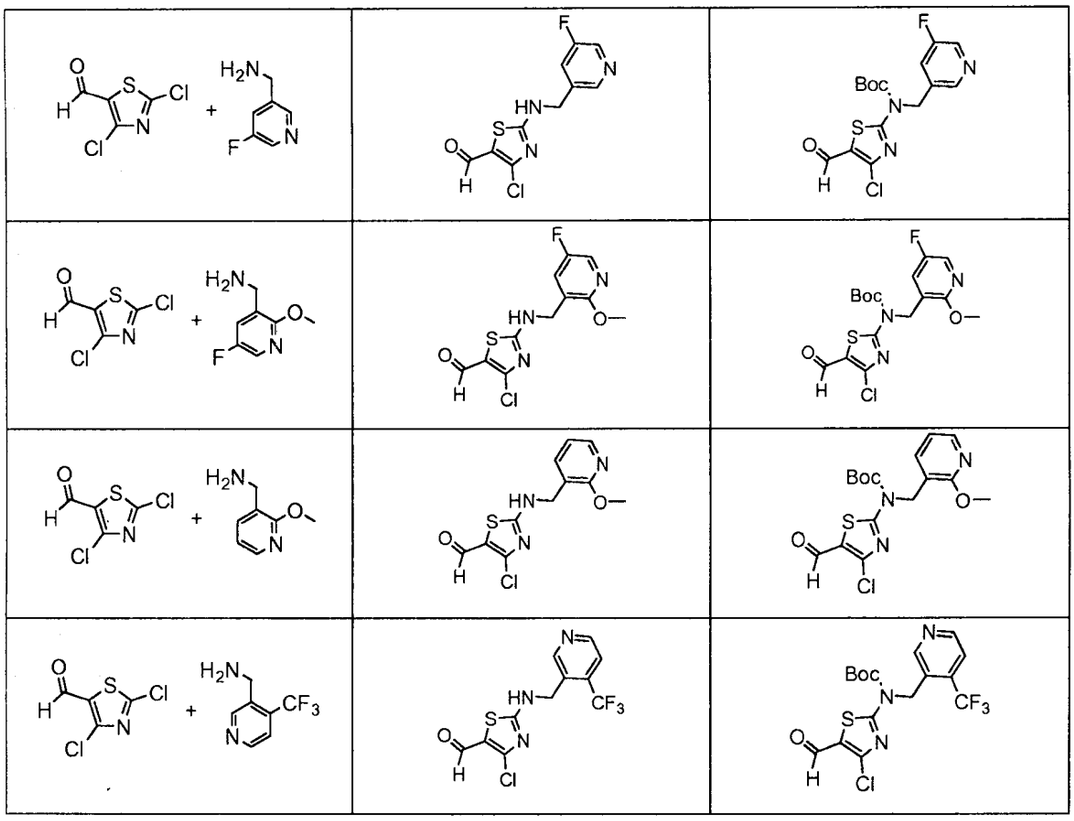
[0311] To a solution of C-(6-trifluoromethyl-pyridin-3-yl)-methylamine (**74**, 1.0 g, 5.7 mmol) and N,N-diisopropylethylamine (2.0 mL, 11 mmol) in 100 mL of tetrahydrofuran, 2,4-dichloro-thiazole-5-carbaldehyde (**73**, 1.1 g, 6.2 mmol) in 10 mL of tetrahydrofuran was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**75**, 1.2 g, 66%). MS (ESI) = $[M+H^+]^+ = 322.11$

*Step 2 – Preparation of (4-chloro-5-formyl-thiazol-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**76**):*

[0312] 4-Chloro-2-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-thiazole-5-carbaldehyde (**75**, 1.2 g, 3.7 mmol), di-tert-butyldicarbonate (**25**, 0.98 g, 4.5 mol), 4-dimethylaminopyridine (0.09 g, 0.7 mmol) and N,N-diisopropylethylamine (0.96 g, 7.5 mmol) were combined in 170 mL of dichloromethane and stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with dichloromethane, washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a yellow solid (**76**, 1.5 g, 95%).

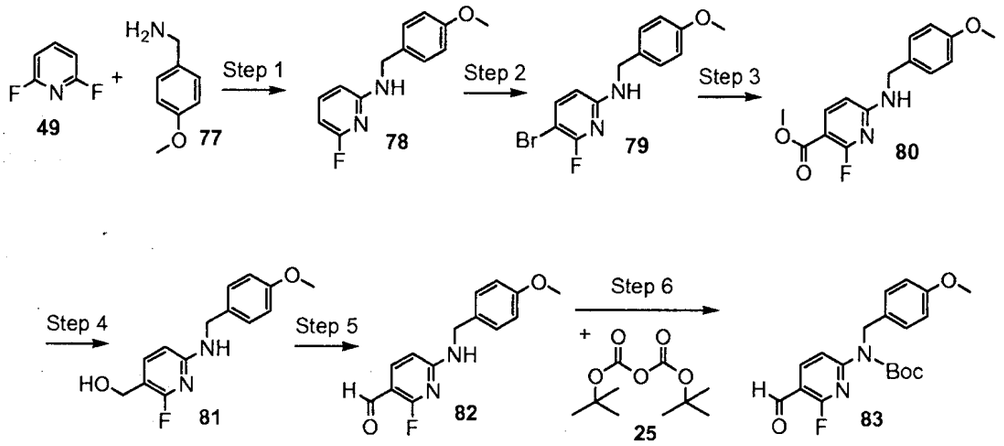
[0313] Additional aldehydes are prepared similarly to the protocol of Scheme 10h, as shown in the following table, where Step 1 and Step 2 reactants are provided in columns 1 and 2, respectively, with the resulting Boc protected aldehyde provided in column 3. Reaction conditions are similar to those described for Scheme 10h, and may vary slightly for each step, for example, any of the solvents, reagents, reaction times, 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. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

Step 1	Step 2	Final aldehyde
		
		
		



[0314] (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **83** was prepared in six steps from 2,6-difluoro-pyridine **49** as shown in Scheme 10i.

Scheme 10i



Step 1 – Preparation of (6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (78):

[0315] To 2,6-difluoro-pyridine (**49**, 100 g, 869 mmol) in 500 mL of N-methylpyrrolidinone, 4-methoxy-benzylamine (**77**, 136 mL, 1.043 mol) and N,N-diisopropylethylamine (304 mL, 1.738

mol) were added. The reaction was stirred at 90 °C overnight, then poured into 8 L of water. The precipitate collected by filtration and washed with water, then taken up in ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was triturated with heptane and collected by filtration to provide the desired compound (**78**, 151 g, 650 mmol, 74.8 % yield).

Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (79):

[0316] To (6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**78**, 151 g, 650 mmol) in 4 L of acetonitrile under nitrogen, N-bromosuccinimide (116 g, 650 mmol) was added in portions. After reacting for 2 hours, the solvent was removed under vacuum and the residue taken up in ethyl acetate, then poured into aqueous sodium thiosulfate. The organic layer was washed with warm water, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was crystallized from heptane to provide the desired compound (**79**, 172 g, 553 mmol, 85 % yield).

Step 3 – Preparation of 2-fluoro-6-(4-methoxy-benzylamino)-nicotinic acid methyl ester (80):

[0317] To (5-bromo-6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine (**79**, 85 g, 273 mmol) in 1.5 L 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) were added. The reaction was heated at 100 °C under 100 psi of carbon monoxide overnight. The reaction was cooled and filtered through celite and the filtrate was concentrated under vacuum. The resulting material was dissolved in dichloromethane and passed through a plug of silica gel, eluting with ethyl acetate. The solvent was removed under vacuum to provide the desired compound as a peach colored solid (**80**, 70 g, 241 mmol, 88 % yield).

Step 4 – Preparation of [2-fluoro-6-(4-methoxy-benzylamino)-pyridin-3-yl]-methanol (81):

[0318] To 2-fluoro-6-(4-methoxy-benzylamino)-nicotinic acid methyl ester (**80**, 70 g, 241 mmol) in 350 mL of tetrahydrofuran, lithium aluminum hydride (362 mL, 1 M in tetrahydrofuran, 362 mmol) was added dropwise while cooling. The reaction was 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. Methyl tert-butyl ether (500 mL) was added and the solids removed by filtration. The filtrate was concentrated under vacuum and the resulting solid was dissolved in dichloromethane, passed through a plug of silica gel and eluted with 50-100% ethyl acetate in heptane. The solvent was removed under vacuum to provide the desired compound as an off-white solid (**81**, 63 g, 240 mmol, 100 % yield).

Step 5 – Preparation of 2-fluoro-6-(4-methoxy-benzylamino)-pyridine-3-carbaldehyde (82):

[0319] To [2-fluoro-6-(4-methoxy-benzylamino)-pyridin-3-yl]-methanol (**81**, 63 g, 240 mmol) in 1.25 L of ethyl acetate, manganese(IV) oxide (210 g, 2.416 mol) was added. The reaction was stirred

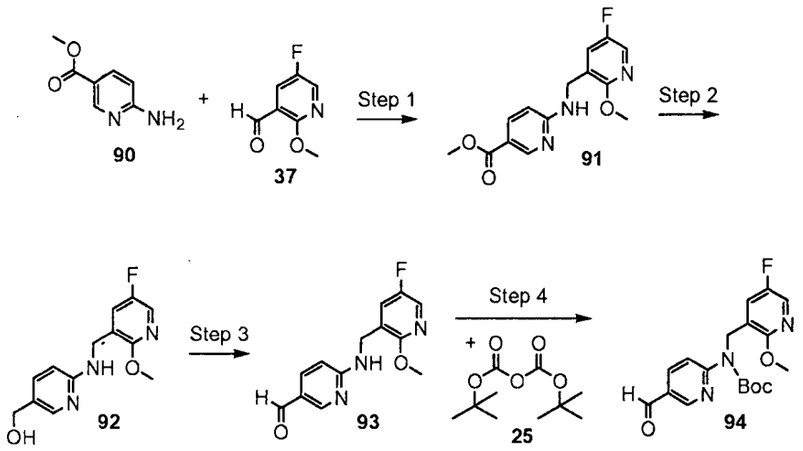
overnight at room temperature, then filtered through celite and the celite rinsed with ethyl acetate. The combined filtrates were concentrated under vacuum and the resulting solid was triturated with heptane and collected by filtration to provide the desired compound as a white solid (**82**, 62 g, 238 mmol, 99% yield).

Step 6 – Preparation of (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (83):

[0320] 2-Fluoro-6-(4-methoxy-benzylamino)-pyridine-3-carbaldehyde (**82**, 62 g, 238 mmol), 600 mL of tert-butyl alcohol, di-tert-butyldicarbonate (**25**, 83 mL, 357 mmol) and dimethylaminopyridine (2.91 g, 23.82 mmol) were combined in a round bottom flask. The reaction was stirred at 30 °C overnight and then concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 0-20% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound (**83**, 54 g, 150 mmol, 62.9 % yield).

[0321] (5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **94** was prepared in four steps from 6-amino-nicotinic acid methyl ester **90** and 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37** as shown in Scheme 10k.

Scheme 10k



Step 1 – Preparation of 6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (91):

[0322] In a round bottom flask, 6-amino-nicotinic acid methyl ester (**90**, 0.678 g, 4.46 mmol) was combined with 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (**37**, 0.532 g, 3.43 mmol), 10.6 mL of acetonitrile, trifluoroacetic acid (1.32 mL, 17.1 mmol) and triethylsilane (3.29 mL, 20.6 mol). The reaction was heated to reflux for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated

under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**91**, 832 mg). MS (ESI) $[M+H^-]^+ = 292.4$.

Step 2 – Preparation of {6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-methanol (92):

[0323] To 6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (**91**, 0.825 g, 2.83 mmol) in 11 mL of tetrahydrofuran, lithium tetrahydroaluminate (5.66 mL, 1.0 M in tetrahydrofuran, 5.66 mmol) was added at -40 oC under nitrogen. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was poured into aqueous 1M sodium hydroxide, then neutralized with aqueous 1M hydrochloric acid. The solids were filtered out through celite, the celite washed with ethyl acetate and tetrahydrofuran. The isolated aqueous layer was extracted with ethyl acetate and all organic layers were combined, washed with brine, then dried over sodium sulfate, filtered and the filtrate was concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**92**, 357 mg). MS (ESI) $[M+H^+]^+ = 264.4$.

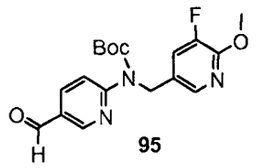
Step 3 – Preparation of 6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (93):

[0324] To {6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-methanol (**92**, 0.353 g, 1.34 mmol) dissolved in 8 mL of tetrahydrofuran, Dess-Maritn periodinane (0.626 g, 1.47 mmol) was added and the reaction stirred at room temperature for 1 hour. The reaction was poured into aqueous saturated sodium thiosulfite and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+ = 262.3$.

Step 4 – Preparation of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (94):

[0325] To 6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (**93**, 0.310 g, 1.19 mmol) dissolved in 4.72 mL of tetrahydrofuran, 4-dimethylaminopyridine (14.5 mg, 0.119 mmol) was added, followed by di-tert-butyldicarbonate (**25**, 0.285 g, 1.30 mmol). The reaction was stirred at room temperature overnight, then concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**94**, 301 mg).

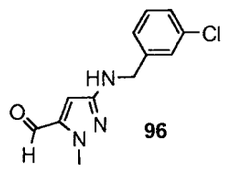
[0326] (5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **95**



95

was prepared similarly to the protocol of Scheme 10k, replacing 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37** with 5-fluoro-6-methoxy-pyridine-3-carbaldehyde in step 1.

[0327] 5-(3-Chloro-benzylamino)-2-methyl-2H-pyrazole-3-carbaldehyde **96**

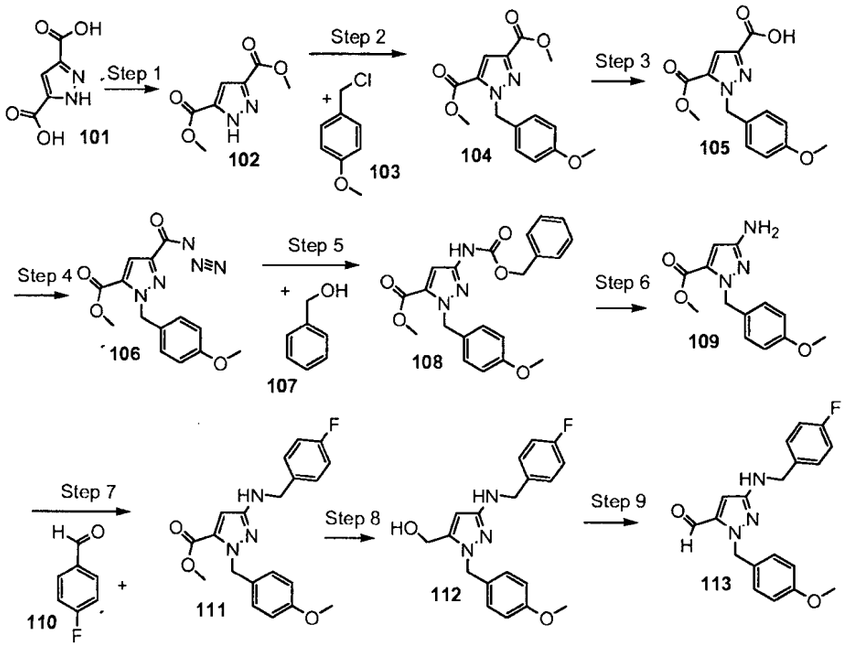


96

was prepared similarly to the protocol of Scheme 10k, steps 1-2 and Scheme 10i, step 3, where 6-amino-nicotinic acid methyl ester **90** was replaced with 5-amino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester and 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37** was replaced with 3-chloro-benzaldehyde in step 1.

[0328] 5-(4-Fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carbaldehyde **113** was prepared in nine steps from 1H-pyrazole-3,5-dicarboxylic acid **101** as shown in Scheme 10n.

Scheme 10n



*Step 1 – Preparation of 1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**102**):*

[0329] In a round bottom flask, 1H-pyrazole-3,5-dicarboxylic acid, hydrate (**101**, 21.1 g, 121 mmol) was combined with 350 mL of methanol and 10 mL of hydrochloric acid was added. The reaction was stirred at reflux overnight and the following day at room temperature. The reaction was concentrated under vacuum and the solid washed with ethyl acetate and hexanes to provide the desired compound. MS (ESI) $[M+H^+]^+ = 185$.

*Step 2 – Preparation of 1-(4-methoxy-benzyl)-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**104**):*

[0330] In a round bottom flask, 1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**102**, 15.0 g, 81.4 mmol) was combined with 1500 mL of acetone and potassium carbonate (15 g, 110 mmol). 1-Chloromethyl-4-methoxy-benzene (**103**, 10.0 mL, 73.8 mmol) was added and the reaction was stirred at 60 °C overnight. The mixture was separated into two flasks and continued stirring for 5 hours. The reactions were concentrated under vacuum and the solids washed with cold water and dried under vacuum to provide the desired compound (**104**, 20.48 g). ^{1}H NMR was consistent with the compound structure.

*Step 3 – Preparation of 1-(4-methoxy-benzyl)-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (**105**):*

[0331] In a round bottom flask, 1-(4-methoxy-benzyl)-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**104**, 28.5 g, 93.6 mmol) was combined with 100 mL of water and 20 mL of 1,4-dioxane. Sulfuric acid (5.5 mL, 100 mmol) and 2.0 mL of water were added and the reaction was stirred for 2 days at 60-70 °C. The reaction was concentrated under vacuum until a precipitate formed. The solid was collected by filtration and washed with cold water several times to provide the desired compound. ^{1}H NMR was consistent with the compound structure.

*Step 4 – Preparation of 5-azidocarbonyl-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**106**):*

[0332] In a round bottom flask, 1-(4-methoxy-benzyl)-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (**105**, 5.48 g, 18.9 mmol) was combined with 20 mL of toluene and thionyl chloride (6 mL, 80 mmol). The reaction was heated at reflux for 40 minutes, then concentrated 2x from toluene and the resulting solid dried under vacuum. This was dissolved in 30.0 mL of acetone and sodium azide (3.8 g, 58 mmol) in 10.0 mL of water was added and stirred for 1 minute. The reaction was poured into 250 mL of ice water and stirred slowly. The resulting precipitate was collected by filtration and dried under vacuum to provide the desired compound.

*Step 5 – Preparation of 5-benzyloxycarbonylamino-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**108**):*

[0333] In a round bottom flask, 5-azidocarbonyl-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**106**, 5.6 g, 18.0 mmol) was combined with 30 mL of toluene and benzyl alcohol (**107**, 1.91 mL, 18.5 mmol) was added and the reaction heated at reflux for 1 hour. The reaction was concentrated under vacuum and the resulting material washed with 2x methanol to provide the desired compound as a white solid. ^{1}H NMR was consistent with the compound structure.

Step 6 – Preparation of 5-amino-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (109):

[0334] In a round bottom flask, 5-benzyloxycarbonylamino-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**108**, 2.3 g, 5.8 mmol) was combined with 30 mL of methanol and 10 mL of tetrahydrofuran under nitrogen and 10% palladium on carbon (0.23 g, 13.0 mmol) was added. The reaction was stirred under hydrogen at 1 atmosphere for 2 hours. The reaction was filtered and the filtrate concentrated under vacuum to provide the desired compound (**109**, 1.4 g).

Step 7 – Preparation of 5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (111):

[0335] In a round bottom flask, 5-amino-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**109**, 1.4 g, 5.4 mmol) was combined with 4-fluoro-benzaldehyde (**110**, 0.565 mL, 5.36 mmol), trifluoroacetic acid (2.06 mL, 26.8 mmol), triethylsilane (4.28 mL, 26.8 mmol) and 50 mL of acetonitrile. The reaction was stirred at room temperature for 15 minutes, then concentrated under vacuum, combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The residue was recrystallized from a mixture of ethyl acetate and hexane to provide the desired compound (**111**, 1.6 g). ^{1}H NMR was consistent with the compound structure.

Step 8 – Preparation of [5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-methanol (112):

[0336] In a round bottom flask, 5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carboxylic acid methyl ester (**111**, 1.6 g, 4.3 mmol) was combined with 100 mL of tetrahydrofuran and cooled to -40 °C. Lithium tetrahydroaluminate (4.8 mL, 1.0 M in tetrahydrofuran, 4.8 mmol) was added and the reaction allowed to warm to 10 °C. The reaction was quenched with sodium sulfate decahydrate, then stirred for 2 hours, filtered through celite and the filtrate concentrated under vacuum. The resulting material was washed with ethyl acetate and hexanes and the solid dried to provide the desired compound. MS (ESI) $[M+H^+]^+ = 342.30$

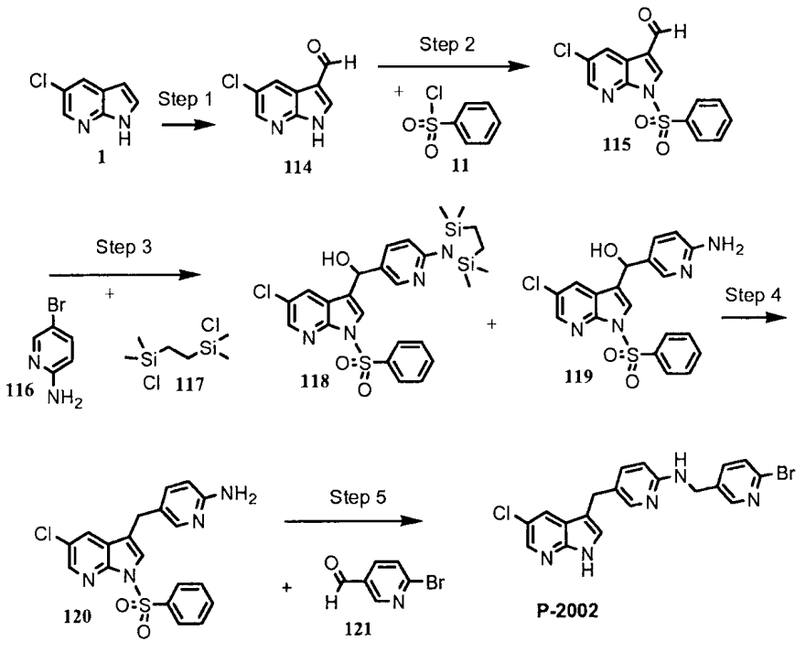
Step 9 – Preparation of 5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carbaldehyde (113):

[0337] In a round bottom flask, [5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-methanol (**112**, 1.6 g, 4.2 mmol) was combined with 300 mL of dichloromethane and manganese(IV) oxide (0.61 g, 7.0 mmol) and stirred overnight under nitrogen. The reaction was filtered through celite and the filtrate concentrated under vacuum. The resulting material was purfied by silica gel column chromatography, eluting with 10-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**113**, 1.4 g). ^{1}H NMR was consistent with the compound structure.

Example 11: Synthesis of (6-bromo-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-2002.

[0338] (6-Bromo-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-2002** was prepared in five steps from 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 11.

Scheme 11



Step 1 – Preparation of 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (114):

[0339] In a round bottom flask, 5-chloro-1H-pyrrolo[2,3-b]pyridine (**1**, 10.0 g, 65.5 mmol) was combined with hexamethylenetetramine (11.9 g, 85.2 mmol), acetic acid (28.3 mL, 0.498 mol) and 56.7 mL of water. The reaction was heated at reflux overnight, then 200 mL of water was added. After 30 minutes, solid material was collected by filtration and dried to give the desired compound (**114**, 7.0 g).

Step 2 – Preparation of 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (115):

[0340] To 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**114**, 3.60 g, 19.9 mmol) in 100 mL of dichloromethane, potassium hydroxide (50 mL, 9M aqueous, 0.45 mol), tetrabutylammonium hydrogen sulfate (400 mg, 1.0 mmol) and benzenesulfonyl chloride (**11**, 2.9 mL, 23.0 mmol) were added. The reaction was stirred at room temperature for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was washed with ethyl acetate to provide the desired compound as a white solid (**115**, 2.3 g).

*Step 3 – Preparation of (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2,2,5,5-tetramethyl-[1,2,5]azadisilolidin-1-yl)-pyridin-3-yl]-methanol (**118**) and (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**119**):*

[0341] In a round bottom flask, 2-amino-5-bromopyridine (**116**, 3.10 g, 17.9 mmol) was combined with 80.0 mL of tetrahydrofuran under nitrogen at -78 °C and n-butyllithium (7.10 mL, 2.50 M in hexane, 17.8 mmol) was slowly added. After 30 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (**117**, 3.90 g, 18.1 mmol) in 20 mL of tetrahydrofuran was added slowly, and the reaction was allowed to come to room temperature over an hour. The reaction was cooled to -78 °C and additional n-butyllithium (7.10 mL, 2.50 M in hexane, 17.8 mmol) was added. The reaction was stirred for 30 minutes at -78 °C and allowed to warm to room temperature over an hour. The reaction was cooled to -78 °C and additional n-butyllithium (7.50 mL, 2.50 M in hexane, 18.8 mmol) was added slowly. After 1 hour, 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**115**, 1.90 g, 5.92 mmol) in 30 mL of tetrahydrofuran was added and the reaction stirred at -78 °C for 2 hours, then allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 2-20% methanol in dichloromethane to provide a mixture of compounds (**118**, 1.7 g) and (**119**, 1.25 g). MS (ESI) $[M+H^+]^+$ = 554.4 for **118** and $[M-H^+]^-$ = 415.2 for **119**.

*Step 4 – Preparation of 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**120**):*

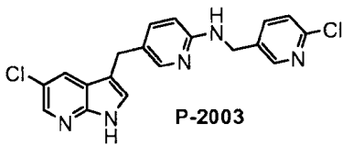
[0342] To (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2,2,5,5-tetramethyl-[1,2,5]azadisilolidin-1-yl)-pyridin-3-yl]-methanol and (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**118**, **119**, 1.70/1.25 g mix, 2.41 mmol) in 25.0 mL of dichloromethane, triethylsilane (3.00 mL, 18.8 mmol) and trifluoroacetic acid (1.50 mL, 19.5 mmol) were added and the reaction stirred at room temperature overnight. The reaction was concentrated under vacuum, combined with aqueous potassium carbonate and extracted with ethyl

acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane to provide the desired compound (**120**, 0.70 g).

*Step 5 – Preparation of (6-bromo-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2002**):*

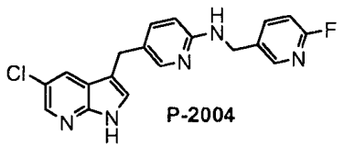
[0343] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**120**, 80.0 mg, 0.200 mmol) in 2.00 mL of ethanol and 0.10 mL of acetic acid, 6-bromo-pyridine-3-carbaldehyde (**121**, 100.0 mg, 0.538 mmol) and silica supported cyanoborohydride (0.50 g, 1.21 mmol/g) were added. The reaction was heated at 110 °C for 25 minutes in microwave. Sodium hydroxide (2.0 mL, 6.0 M aqueous) was added and the reaction heated at 100 °C for 10 minutes in microwave, then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane. Appropriate fractions were combined and the solvent removed under vacuum to provide the desired compound (**P-2002**, 26.6 mg). MS (ESI) $[M+H^+]^+$ = 427.7, 429.7.

[0344] (6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-2003**, and [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine **P-2004**,



P-2003

, and



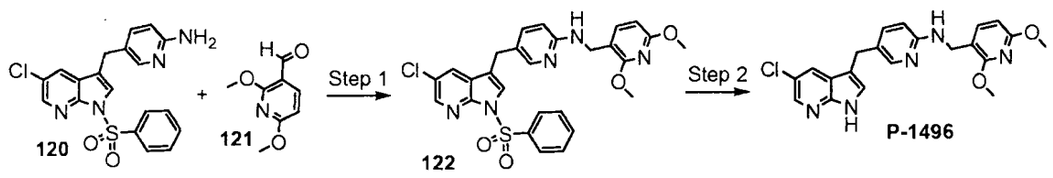
P-2004

were prepared similarly to the protocol of Scheme 11, replacing 6-bromo-pyridine-3-carbaldehyde **121** with 6-chloro-pyridine-3-carbaldehyde and 6-fluoro-pyridine-3-carbaldehyde, respectively. MS (ESI) $[M+H^+]^+$ = 383.9, 385.9 (**P-2003**) and 367.9, 368.9 (**P-2004**).

Example 12: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amineP-1496.

[0345] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine **P-1496** was prepared in two steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **120** and 2,6-dimethoxy-pyridine-3-carbaldehyde **121** as shown in Scheme 12.

Scheme 12



*Step 1 – Preparation of [5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**122**):*

[0346] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**120**, 60.0 mg, 0.150 mmol) in 2.0 mL of ethanol and 0.1 mL of acetic acid, 2,6-dimethoxy-pyridine-3-carbaldehyde (**121**, 120 mg, 0.75 mmol) and silica supported cyanoborohydride (0.40 g, 0.484 mmol) were added. The reaction was heated to 100 °C for 18 minutes at 300 Watts in microwave, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20 % ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**122**, 60 mg).

*Step 2 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**P-1496**):*

[0347] To [5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**122**, 60 mg, 0.11 mmol) in 10.0 mL of methanol, potassium hydroxide (0.20 g, 3.6 mmol) was added. The reaction was stirred at 60 °C for 4 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**P-1496**, 26.1 mg). MS (ESI) $[M+H^+]^+ = 410.0$.

[0348] Additional compounds are prepared following the protocol of Scheme 12, where 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. For example, without limitation, tetrabutylammonium fluoride trihydrate is used in place of potassium hydroxide in step 2. Compounds are prepared optionally substituting 2,6-dimethoxy-pyridine-3-carbaldehyde **121** with a suitable aldehyde and optionally substituting 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **120** with a suitable 1-benzenesulfonyl protected 1H-pyrrolo[2,3-b]pyridine. The following compounds are made using this procedure. Compounds in the following table were characterized by ^1H and ^{13}C NMR

spectroscopy as well as mass spectrometry.

(6-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1498**),

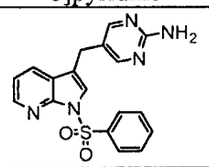
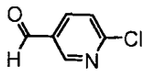
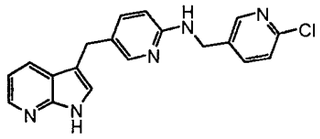
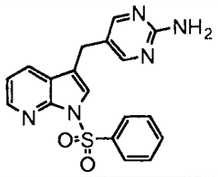
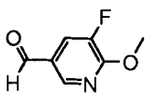
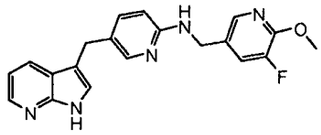
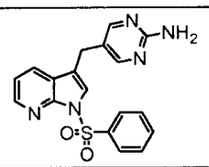
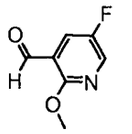
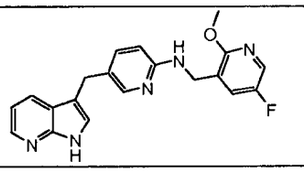
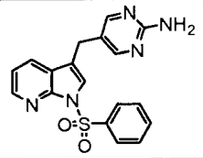
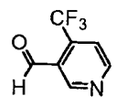
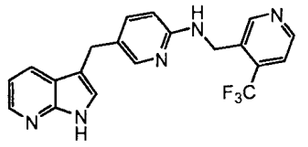
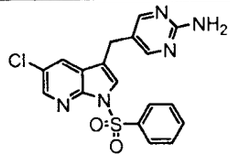
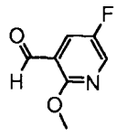
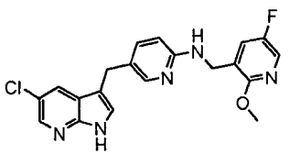
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1502**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1503**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1504**), and

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1505**).

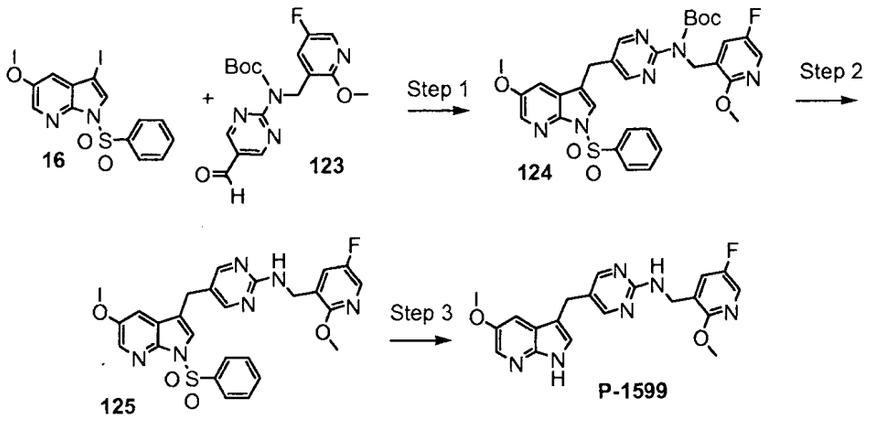
The following table indicates the 1-benzenesulfonyl protected 1H-pyrrolo[2,3-b]pyridine (column 2) and aldehyde compound (column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Comp. number	1H-pyrrolo[2,3-b]pyridine	Aldehyde structure	Compound structure	MS (ESI) $[M+H^+]^+$
P-1498				
P-1502				
P-1503				
P-1504				
P-1505				

Example 13: Synthesis of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine P-1599.

[0349] (5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-1599** is prepared in three steps from 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **16** and (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyrimidin-2-yl)-carbamic acid tert-butyl ester **123** as shown in Scheme 13.

Scheme 13



Step 1 – Preparation of {5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyrimidin-2-yl}-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (124):

[0350] To a solution of 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**16**, 1 equivalent) in 4.0 mL of tetrahydrofuran, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 1 equivalent) is added slowly at -50 °C. The reaction is allowed to warm to 5 °C over 70 minutes, then cooled to -45 °C and (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyrimidin-2-yl)-carbamic acid tert-butyl ester (**123**, 0.78 equivalent) in 2.0 mL of tetrahydrofuran is added. The reaction is allowed to warm to room temperature over 1 hour, then poured into aqueous ammonium chloride and extracted with ethyl ether. 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.

Step 2 – Preparation of [5-(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (125):

[0351] To {5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyrimidin-2-yl}-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**124**, 1 equivalent) in 10.0 mL of acetonitrile, triethylsilane (15.6 equivalents) and trifluoroacetic acid (16.9

equivalents) are added. The reaction is heated 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 to provide the desired compound, which is used in the next step without further purification.

*Step 3 – Preparation of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1599**):*

[0352] To [5-(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**125**, 1 equivalent) in 15.0 mL of tetrahydrofuran, tetrabutylammonium fluoride trihydrate (2 equivalent) 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 combined and concentrated under vacuum to provide the desired compound as a yellow solid.

[0353] Additional compounds are prepared following the protocol of Scheme 13, where 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. Compounds are prepared using a suitable Boc protected aldehyde in place of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-(5-formyl-pyrimidin-2-yl)-carbamic acid tert-butyl ester **123** in step 1. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1600**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1601**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1602**),

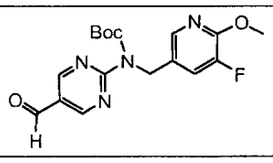
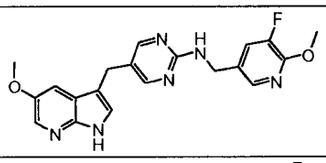
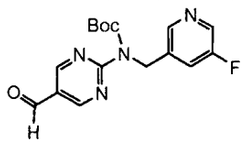
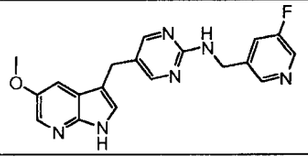
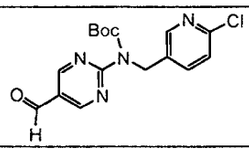
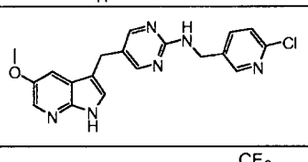
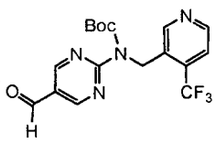
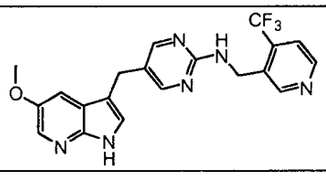
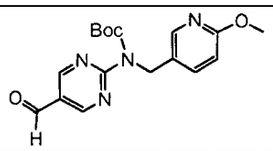
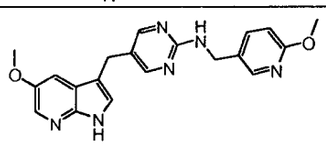
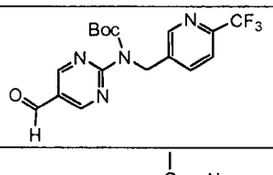
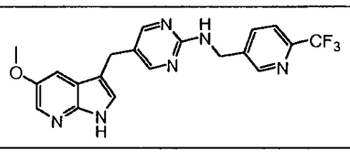
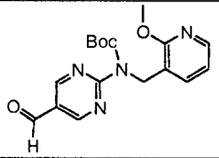
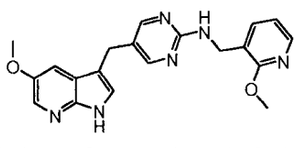
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1603**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1604**),

[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1605**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1606**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),** and
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204)**.

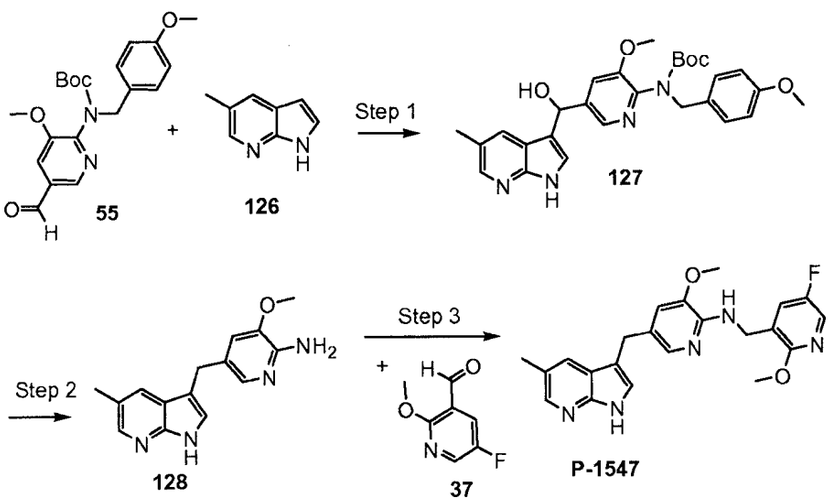
The following table indicates the aldehyde compound (column 2) used in step 1 to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	Aldehyde	Compound structure	MS (ESI) $[M+H^+]^+$
P-1600			
P-1601			
P-1602			
P-1603			
P-1604			
P-1605			
P-1606			

Example 14: Synthesis of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-1547.

[0354] (5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-1547** is prepared in three steps from (5-formyl-3-methoxy-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **55** and 5-methyl-1H-[2,3-b]pyridine **126** as shown in Scheme 14.

Scheme 14



Step 1 – Preparation of {5-[hydroxy-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-3-methoxy-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (127):

[0355] In a vial, 5-methyl-1H-[2,3-b]pyridine (**126**, 1 equivalent) is combined with (5-formyl-3-methoxy-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**55**, 1.1 equivalents), 5 mL of methanol, and potassium hydroxide (3 equivalents). The reaction is stirred at room temperature overnight, then aqueous 1N hydrochloric acid is added and the mixture is extracted with ethyl acetate. The organic layer is washed with water, brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with methanol and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound.

Step 2 – Preparation of 3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (128):

[0356] In a round bottom flask, {5-[hydroxy-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-3-methoxy-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**127**, 1 equivalent) is combined with 100 mL of acetonitrile, triethylsilane (18 equivalents), and trifluoroacetic acid (18 equivalents). The reaction is heated at reflux for 24 hours, then concentrated under vacuum. The

resulting material is dissolved in 40 mL of trifluoroacetic acid and stirred at room temperature for 18 hours. This is concentrated under vacuum and combined with water and sodium bicarbonate, then extracted with ethyl acetate. The organic layer is washed with sodium bicarbonate, water, brine, then dried with magnesiuim sulfate, filtered and the filtrate is concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound.

*Step 3 – Preparation of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1547**):*

[0357] To 3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**128**, 1 equivalent) in 2 mL of acetonitrile, 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (**37**, 1 equivalent), triethylsilane (5 equivalents) and trifluoroacetic acid (6.9 equivalents) are added. The reaction is heated at 80 °C for 18 hours, then concentrated under vacuum and mixed with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer is washed with water, brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material is purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound.

[0358] Additional compounds are prepared following the protocol of Scheme 14, where 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. Compounds are prepared using a suitable aldehyde in place 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37** in step 3. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1548**),

(5-Fluoro-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1549**),

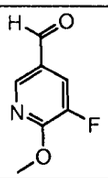
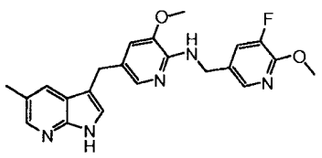
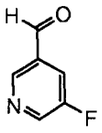
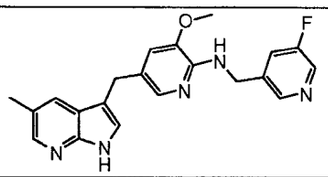
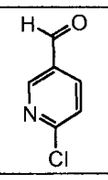
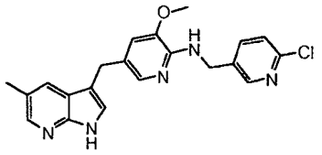
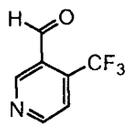
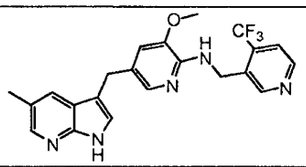
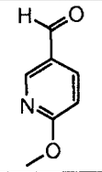
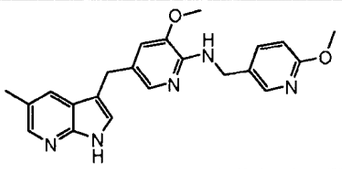
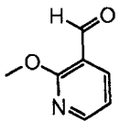
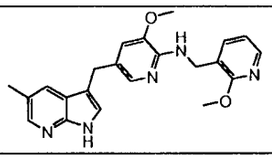
(6-Chloro-pyridin-3-ylmethyl)-[3-methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1550**),

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1551**),

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1552**), and

[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1553**).

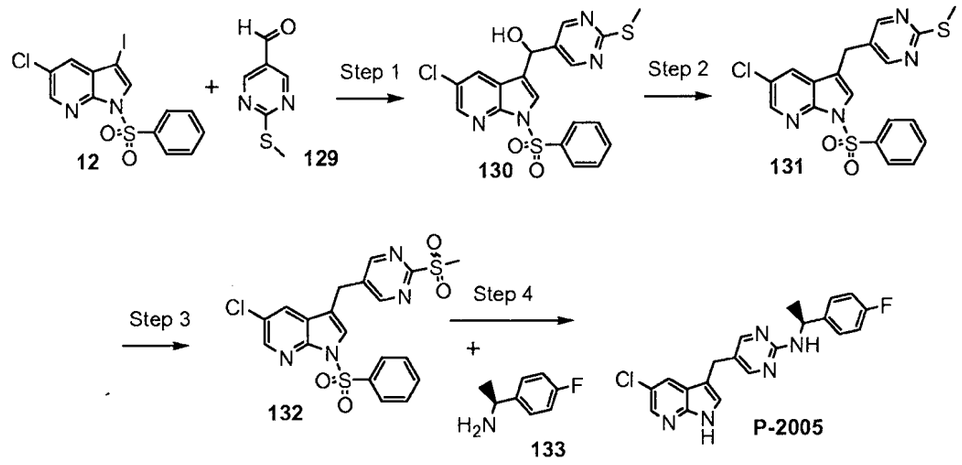
The following table indicates the aldehyde compound (column 2) used in step 3 to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	Aldehyde	Compound	MS (ESI) $[M+H^+]^+$
P-1548			
P-1549			
P-1550			
P-1551			
P-1552			
P-1553			

Example 15: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine P-2005.

[0359] [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine **P-2005** was prepared in 4 steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **12** and 2-methylsulfanyl-pyrimidine-5-carbaldehyde **129** as shown in Scheme 15.

Scheme 15



*Step 1 – Preparation of (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**130**):*

[0360] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**12**, 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) was added slowly. The reaction was allowed to warm to 5 °C over 60 minutes, then cooled to -40 °C, followed by addition of 2-methylsulfanyl-pyrimidine-5-carbaldehyde (**129**, 2.50 g, 16.2 mmol) in 15.0 mL of tetrahydrofuran. The reaction was allowed to warm to 10 °C over 2 hours, then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 40-100% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound as an off-white solid (**130**, 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 (**131**):*

[0361] To (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**130**, 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) were added. The reaction was stirred at 80 °C for 3 hours, then concentrated under vacuum and mixed with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and solvents removed under vacuum to provide the desired compound (**131**, 2.90 g).

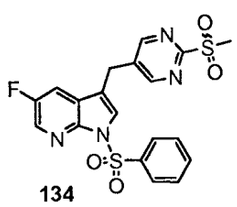
Step 3 – Preparation of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (132):

[0362] To 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**131**, 4.40 g, 10.2 mmol) in 100.0 mL of dichloromethane, meta-chloroperoxybenzoic acid (max. 77%, 4.90 g, 21.9 mmol) was added at 0 °C. The reaction was stirred at 0 °C for 40 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and the filtrate was concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane. Appropriate fractions were combined and solvents removed under vacuum to provide the desired compound (**132**, 3.76 g). MS (ESI) $[M+H^+]^+ = 463.0$.

*Step 4 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-2005**):*

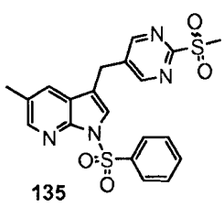
[0363] In a microwave vial, 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**132**, 12 mg, 0.026 mmol) was mixed with 600 µL of N-methylpyrrolidinone and (S)-1-(4-fluoro-phenyl)-ethylamine (**133**, 25.2 mg, 0.18 mmol). The reaction was irradiated at 200 °C for 40 minutes in microwave, then potassium hydroxide (500 µL, 4.00 M in water) was added and the reaction irradiated at 90 °C for 10 minutes in microwave. The reaction was neutralized with the addition of 120 µL of acetic acid, solvents were removed under vacuum, and the resulting material was dissolved in 400 µL of dimethyl sulfoxide for purification by HPLC. The desired compound was purified on Phenomenex C18 column (50mm x 10 mm ID) with mobile phase A of 0.1% trifluoroacetic acid in water, mobile phase B of 0.1% trifluoroacetic acid in acetonitrile, 20-100% B over 16 minutes at a flow rate of 6 mL/min. Appropriate fractions were collected and solvents removed under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+ = 381.9$.

[0364] 1-Benzenesulfonyl-5-fluoro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **134** and 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-5-methyl-1H-pyrrolo[2,3-b]pyridine **135**



134

and



135

are similarly prepared following the protocol of Scheme 15, steps 1-3, replacing 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **12** with 1-benzenesulfonyl-5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine or 1-benzenesulfonyl-3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine respectively in step 1. These are used following the protocol of Scheme 15 step 4 to make additional compounds. In some

instances for the 5-fluoro substituted compounds, removal of the benzenesulfonyl protecting group is done in an additional step by reacting with tetrabutylammonium fluoride trihydrate in tetrahydrofuran.

[0365] Additional compounds are prepared following the protocol of Scheme 15, step 4, where 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. Compounds are prepared substituting (S)-1-(4-fluoro-phenyl)-ethylamine **133** with a suitable amine and optionally substituting 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **132** with 1-benzenesulfonyl-5-fluoro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **134** or 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-5-methyl-1H-pyrrolo[2,3-b]pyridine **135**. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(3-Chloro-4-methyl-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2007**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,4-difluoro-benzyl)-amine (**P-2008**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl)-amine (**P-2009**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethoxy-benzyl)-amine (**P-2010**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-amine (**P-2011**),

(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-2012**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-methyl-benzyl)-amine (**P-2013**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-4-methyl-benzyl)-amine (**P-2014**),

[2-(3-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2015**),

[2-(2-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2020**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[2-(4-fluoro-phenyl)-ethyl]-amine (**P-2021**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[2-(6-methyl-pyridin-2-yl)-

ethyl]-amine (**P-2022**),

Butyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2026**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(1-thiazol-2-yl-ethyl)-amine (**P-2039**),

[1-(4-Fluoro-phenyl)-propyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2053**),

[1-(4-Fluoro-phenyl)-cyclopropyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2055**),

[(S)-1-(4-Fluoro-phenyl)-ethyl]-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2056**),

(2-Methoxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2069**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-4-ylmethyl)-amine (**P-2074**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-2076**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-2077**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2078**),

(6-Methyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2079**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2080**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-2081**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2082**),

(5-Ethyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2083**),

(3-Methyl-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2084**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-pyridin-4-ylmethyl)-amine (**P-2085**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine (**P-2138**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

amine (**P-2139**),

[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylmethyl]-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2140**),

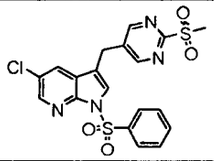
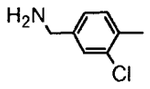
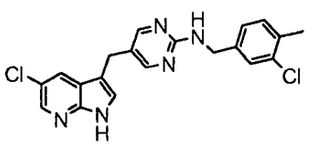
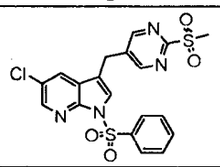
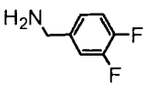
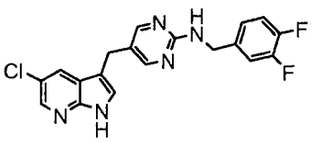
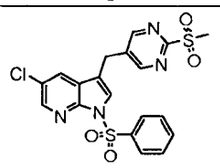
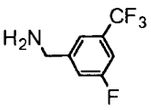
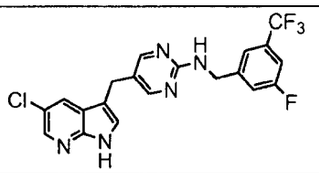
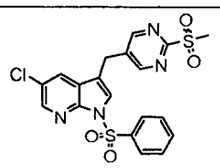
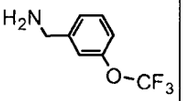
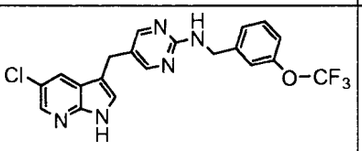
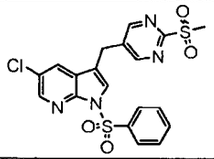
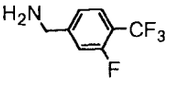
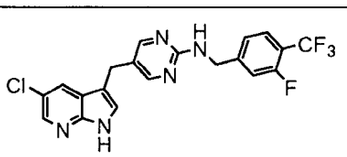
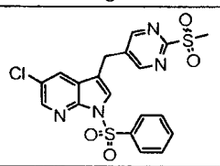
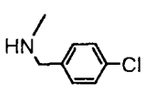
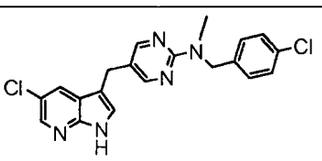
(2-Methyl-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2141**),

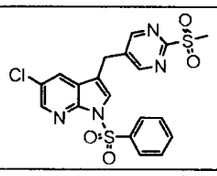
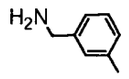
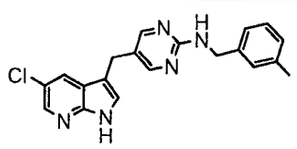
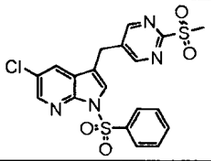
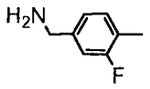
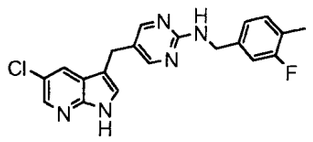
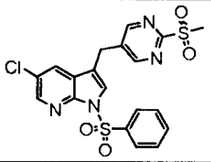
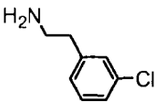
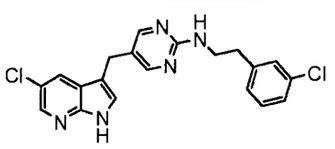
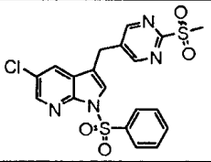
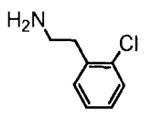
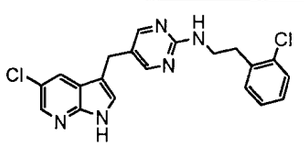
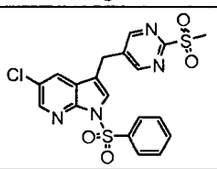
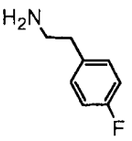
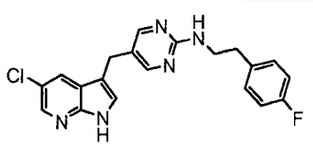
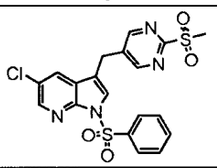
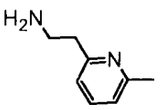
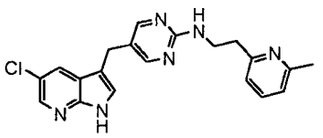
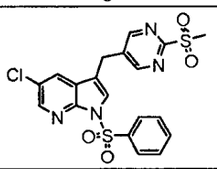
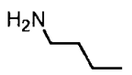
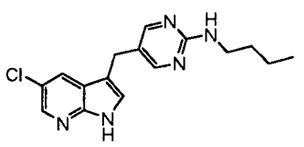
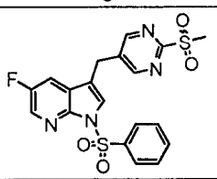
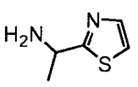
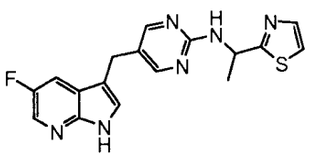
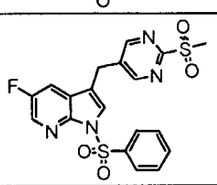
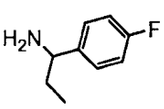
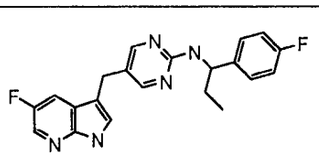
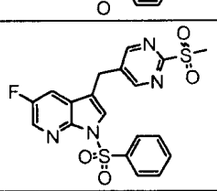
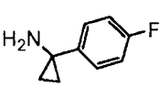
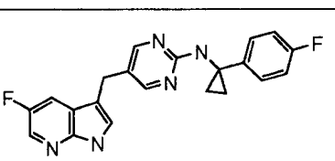
(2-Ethoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2142**),

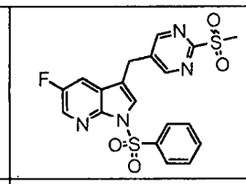
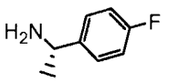
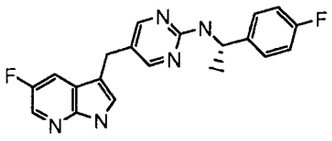
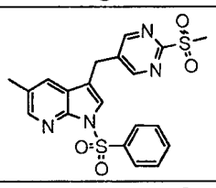
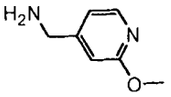
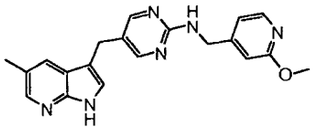
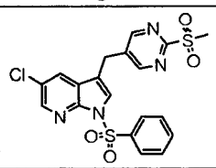
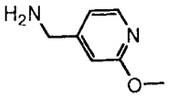
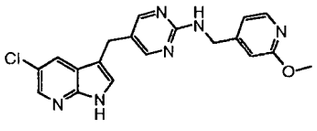
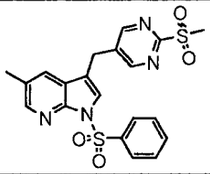
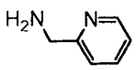
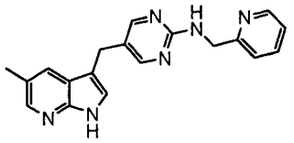
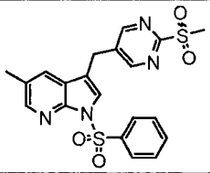
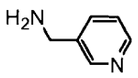
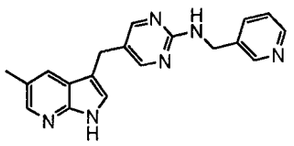
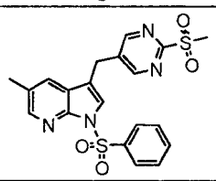
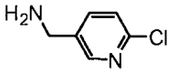
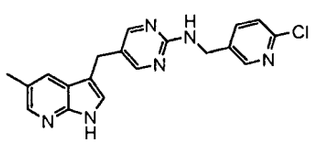
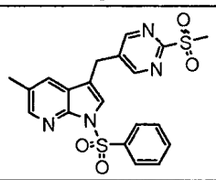
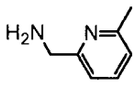
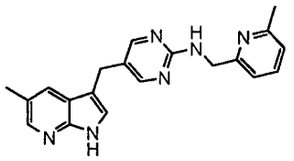
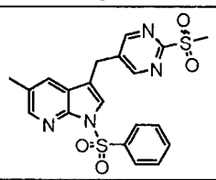
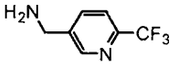
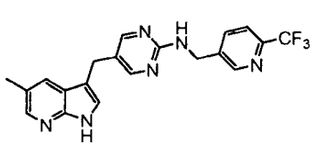
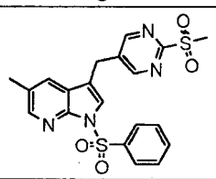
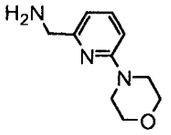
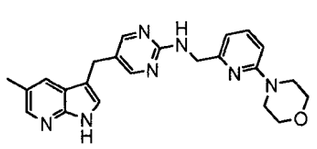
(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2148**), and

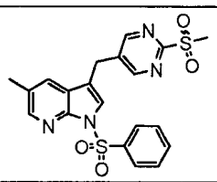
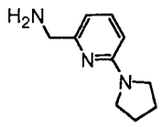
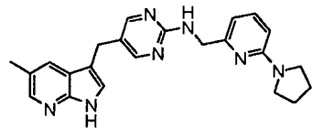
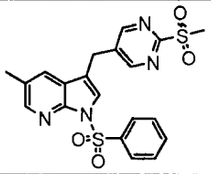
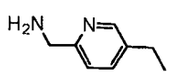
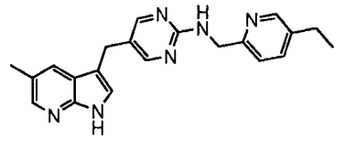
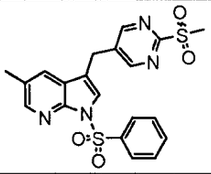
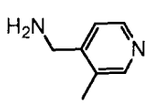
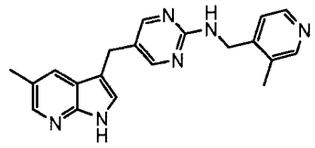
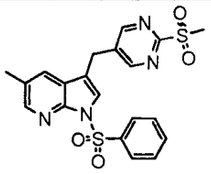
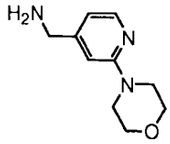
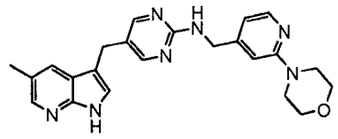
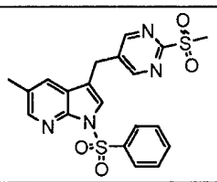
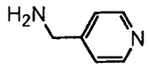
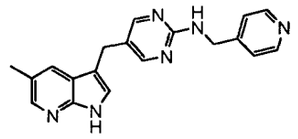
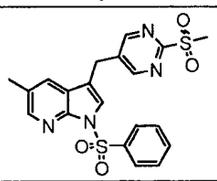
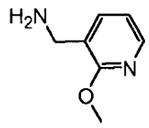
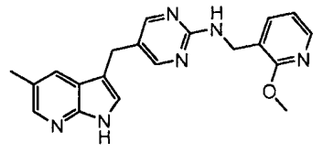
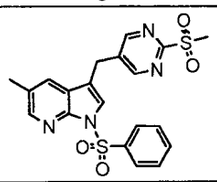
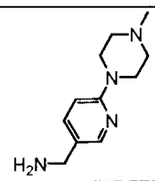
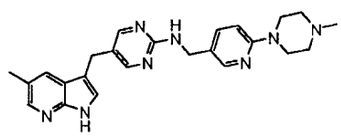
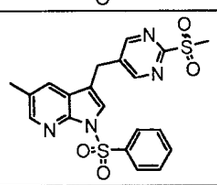
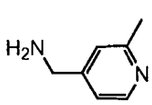
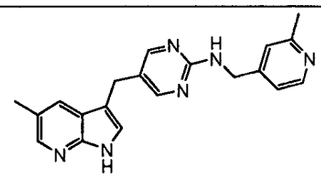
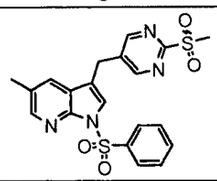
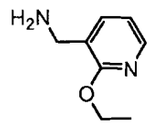
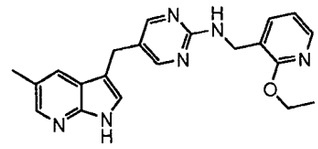
(2-Cyclopentyloxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2149**).

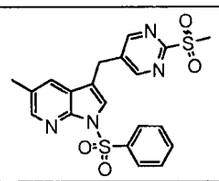
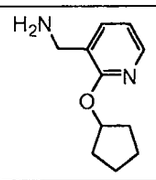
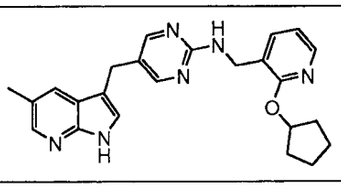
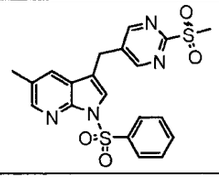
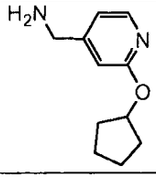
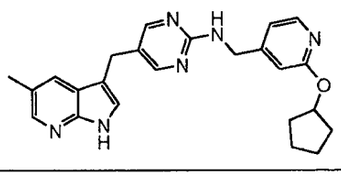
The following table indicates the 1H-pyrrolo[2,3-b]pyridine (column 2) and the amine compound (column 3) used in step 4 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Comp. number	1H-pyrrolo[2,3-b]pyridine	Amine structure	Compound structure	MS (ESI) $[M+H^+]^+$
P-2007				397.9
P-2008				386.3
P-2009				436.3
P-2010				434.3
P-2011				435.9
P-2012				

P-2013				364.3
P-2014				381.9
P-2015				397.9
P-2020				397.9 399.95
P-2021				384.0
P-2022				379.4
P-2026				
P-2039				
P-2053				
P-2055				377.9

P-2056				366.0
P-2069				
P-2074				380.9
P-2076				
P-2077				
P-2078				365.1
P-2079				345.1
P-2080				
P-2081				416.3

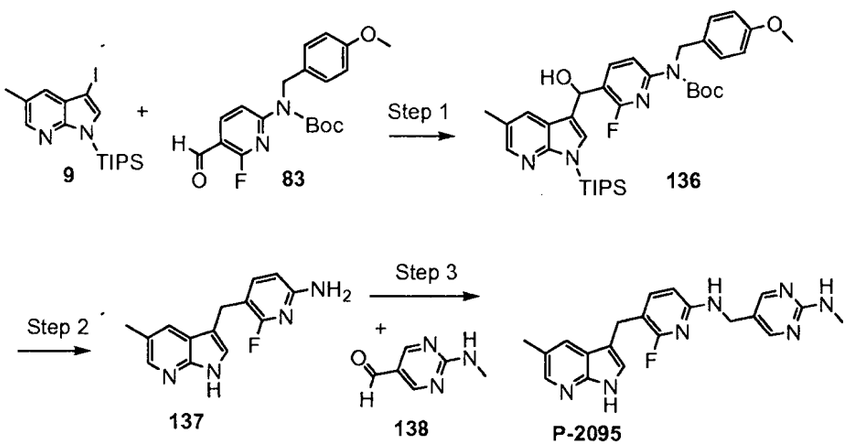
P-2082				400.3
P-2083				
P-2084				
P-2085				
P-2138				
P-2139				361.5
P-2140				
P-2141				
P-2142				

P-2148				415.5
P-2149				

Example 16: Synthesis of (5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-methyl-amine P-2095.

[0366] (5-{[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-methyl-amine **P-2095** was prepared in three steps from 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **9** and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **83** as shown in Scheme 16.

Scheme 16



*Step 1 – 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 (**136**):*

[0367] To 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**9**, 40 g, 97.0 mmol) in 400 mL of tetrahydrofuran under nitrogen at -20 °C, isopropylmagnesium chloride (54.8 mL, 2 M in tetrahydrofuran, 110 mmol) was added and the reaction allowed to warm to 0 °C over 30 minutes. The reaction was cooled to -40 °C and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**83**, 15.81 g, 43.9 mmol) in tetrahydrofuran was added. The reaction was allowed to warm to 0 °C over an hour, then quenched with brine and extracted with ethyl acetate. The organic

layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 0-40% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound (**136**, 21 g, 32.4 mmol, 73.8 % yield).

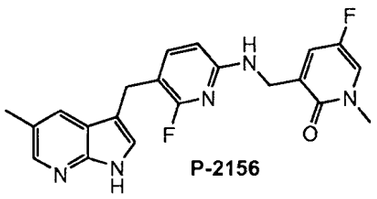
Step 2 – Preparation of 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (137):

[0368] 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 (**136**, 21 g, 32.4 mmol) in 500 mL of acetonitrile, triethylsilane (51.7 mL, 324 mmol) and trifluoroacetic acid (24.93 mL, 324 mmol) were added. The reaction was stirred at 50 °C for several hours, solvents removed under vacuum, and the residue taken up in 250 mL of dichloromethane and 250 mL of trifluoroacetic acid was added. The mixture was stirred at reflux for several hours, then concentrated under vacuum. The residue was taken up in ethyl acetate and poured into aqueous potassium carbonate. The organic layer was separated, concentrated under vacuum and purified by silica gel column chromatography, eluting with 0-5% methanol in dichloromethane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound (**137**, 5.2 g, 20.29 mmol, 62.7 % yield).

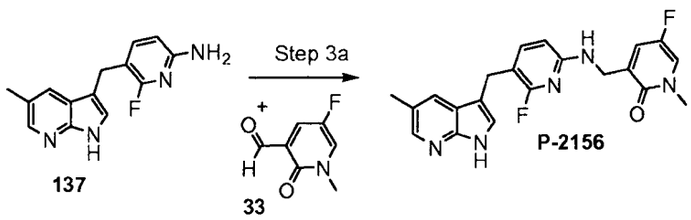
*Step 3 – Preparation of (5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-methyl-amine (**P-2095**):*

[0369] In a 2 mL microwave vial, 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**137**, 9.72 mg, 0.04 mmol) and 2-methylamino-pyrimidine-5-carbaldehyde (**138**, 11.0 mg, 0.08 mmol) were dissolved in 600 µL of 95:5 ethanol:acetic acid, and silica supported cyanoborohydride (50 mg, 1mmol/g, 0.05 mmol) was added. The reaction was irradiated for 10 minutes at 160 °C in a microwave. The vial was centrifuged to condense the silica and the supernatant was removed by pipette into another vial. The residual silica was rinsed with 500 µL of ethanol, centrifuged and the supernatant added to the first supernatant. The solvents were removed under vacuum and the resulting material dissolved in 400 µL of dimethyl sulfoxide for purification by HPLC. Samples were purified on Phenomenex C18 column (50mm x 10 mm ID) with mobile phase A of 0.1% trifluoroacetic acid in water, mobile phase B of 0.1% trifluoroacetic acid in acetonitrile, 20-100% B over 16 minutes at a flow rate of 6 mL/min. Appropriate fractions were collected and solvents removed under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+ = 378.3$.

[0370] 5-Fluoro-3-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-1-methyl-1H-pyridin-2-one **P-2156**



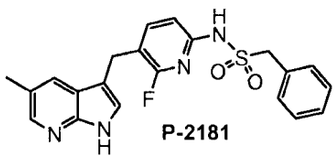
was prepared similarly to the protocol of Scheme 16, where step 3 was replaced by the following step 3a:



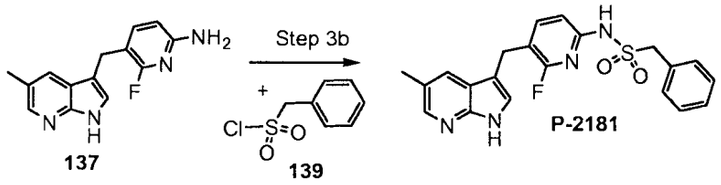
*Step 3a – Preparation of 5-fluoro-3-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-1-methyl-1H-pyridin-2-one (**P-2156**):*

[0371] To 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**137**, 3.99 g, 15.59 mmol) and 5-fluoro-1-methyl-2-oxo-1,2-dihydro-pyridine-3-carbaldehyde (**33**, 2.66 g, 17.15 mmol) in 50 mL of acetonitrile, triethylsilane (9.96 mL, 62.4 mmol) and trifluoroacetic acid (4.80 mL, 62.4 mmol) were added. The reaction was stirred at 80 °C for several hours, then concentrated under vacuum and the residue was taken up in ethyl acetate and poured into aqueous potassium carbonate. The organic layer was separated, concentrated under vacuum, and the residue purified by silica gel column chromatography, eluting with 0-5% methanol in dichloromethane. Appropriate fractions were combined and concentrated under vacuum, and the residue triturated with methanol to provide the desired compound (**P-2156**, 3.1 g, 7.84 mmol, 50.3 % yield).

[0372] N-[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-C-phenyl-methanesulfonamide **P-2181**



similarly to the protocol of Scheme 16, where step 3 was replaced by the following step 3b:



*Step 3b – Preparation of N-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-C-phenyl-methanesulfonamide (**P-2181**):*

[0373] In a vial, 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**137**, 157 mg, 0.614 mmol) was mixed with 4 mL of dichloromethane and pyridine (149 μL, 1.84 mmol) and cooled to 0 °C in an ice water bath. Phenyl-methanesulfonyl chloride (**139**, 0.234 g, 1.23 mmol) was added and the reaction stirred at 0 °C for 1 hour, then warmed to room temperature and stirred overnight. Aqueous saturated sodium bicarbonate was added and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 0-10% methanol in dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a yellow solid (**P-2181**, 39 mg). MS (ESI) $[M+H^+]^+ = 411.1$.

[0374] Additional compounds are prepared following the protocol of Scheme 16 (step 3a may be substituted for step 3) where 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. Compounds are prepared optionally substituting 3-iodo-5-methyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **9** with a suitable 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine in step 1; optionally replacing (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **83** with (5-formyl-pyrimidin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester in step 1; and optionally replacing 2-methylamino-pyrimidine-5-carbaldehyde **138** with a suitable aldehyde in step 3. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1569**),

[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1570**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1611**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1612**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1613**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1614**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1646**),

(5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1647**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1648**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1649**),
[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1650**),
[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1651**),
[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1652**),
[6-Fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1653**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2064**),
(2,5-Dimethoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2086**),
(3,5-Dimethoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2087**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2088**),
(3-Bromo-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2089**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-morpholin-4-yl-pyridin-3-ylmethyl)-amine (**P-2090**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-morpholin-4-yl-pyridin-3-ylmethyl)-amine (**P-2091**),
(3-Chloro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2092**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-2093**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-fluoro-pyridin-4-

ylmethyl)-amine (**P-2094**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-2096**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2097**),
(5-Fluoro-2-methanesulfonyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2098**),
(5-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2099**),
(5-Bromo-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2100**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-methyl-pyridin-4-ylmethyl)-amine (**P-2101**),
(3-Chloro-5-fluoro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2102**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-3-ylmethyl)-amine (**P-2103**),
(3,5-Dimethyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2104**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-2105**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyrimidin-5-ylmethyl)-amine (**P-2106**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methylamino-pyridin-3-ylmethyl)-amine (**P-2107**),
(3,5-Bis-trifluoromethyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2108**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-methoxy-pyridin-3-ylmethyl)-amine (**P-2109**),
(2-Ethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2110**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-isopropoxy-pyridin-3-ylmethyl)-amine (**P-2111**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-methyl-pyridin-2-ylmethyl)-amine (**P-2112**),
(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2113**),

(2-Cyclohexyloxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2114**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2115**),
(2-Chloro-5-fluoro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2116**),
4-{[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridine-2-carbonitrile (**P-2117**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-4-ylmethyl)-amine (**P-2118**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-pyridin-4-ylmethyl)-amine (**P-2119**),
(2-Chloro-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2120**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-morpholin-4-yl-pyridin-4-ylmethyl)-amine (**P-2121**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-pyrrolidin-1-yl-pyridin-4-ylmethyl)-amine (**P-2122**),
(5-Chloro-2-fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2123**),
(4-Chloro-2-methanesulfonyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2124**),
(2-Dimethylamino-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2125**),
(2-Ethyl-pyrimidin-5-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2126**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-propyl-pyrimidin-5-ylmethyl)-amine (**P-2127**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-isopropyl-pyrimidin-5-ylmethyl)-amine (**P-2128**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2-methoxy-ethyl)-pyrimidin-5-ylmethyl]-amine (**P-2129**),
(2-Butyl-pyrimidin-5-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2130**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methyl-pyridin-2-ylmethyl)-amine (**P-2131**),
(3-Fluoro-5-methyl-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-

yl]-amine (**P-2132**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3-methoxy-5-trifluoromethyl-benzyl)-amine (**P-2133**),

(3-Fluoro-5-methoxy-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2134**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(3,4,5-trimethoxy-benzyl)-amine (**P-2150**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2151**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2166**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-dimethylamino-6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2167**),

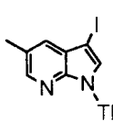
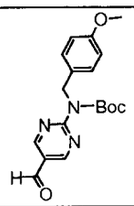
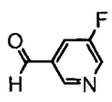
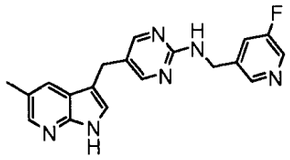
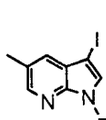
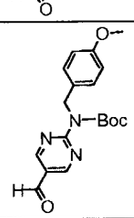
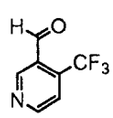
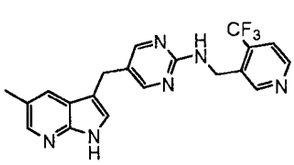
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2186**),

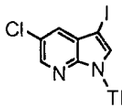
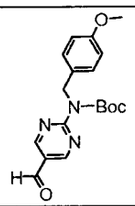
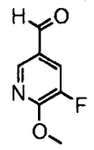
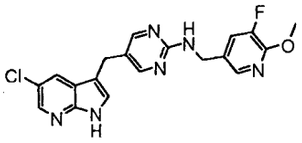
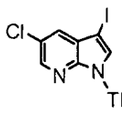
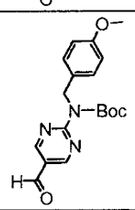
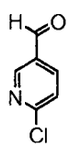
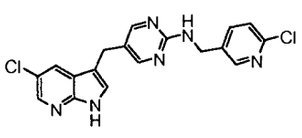
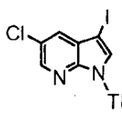
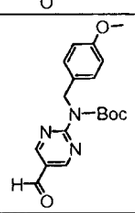
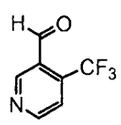
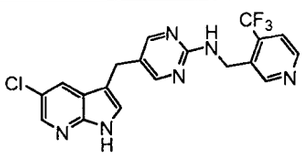
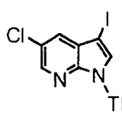
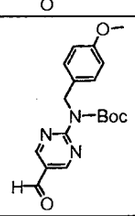
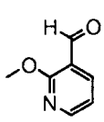
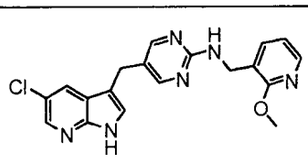
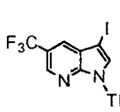
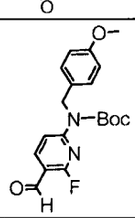
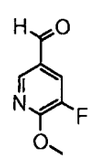
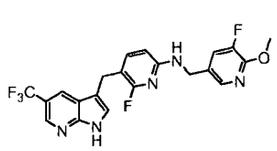
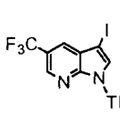
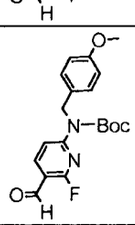
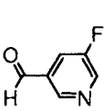
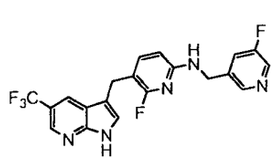
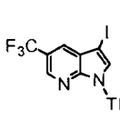
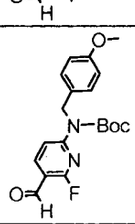
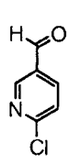
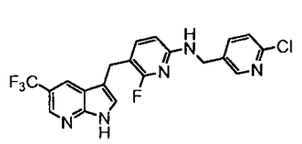
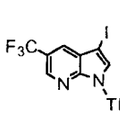
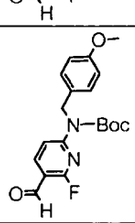
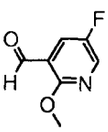
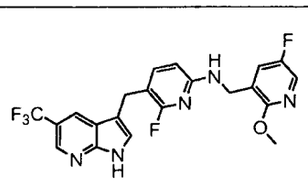
Ethanesulfonic acid (2-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2198**),

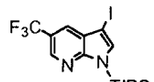
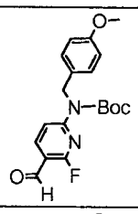
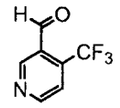
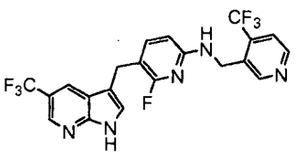
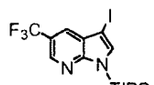
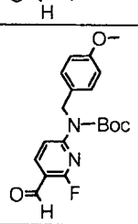
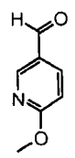
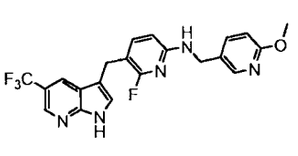
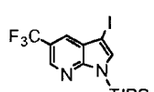
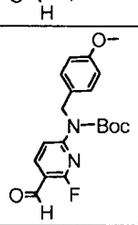
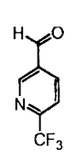
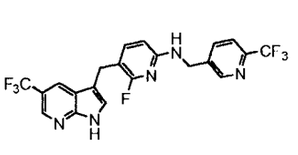
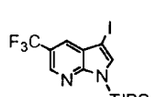
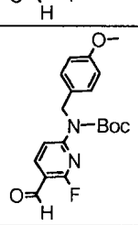
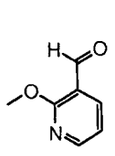
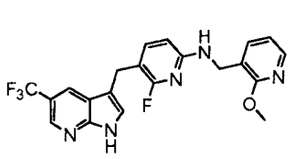
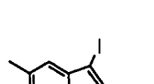
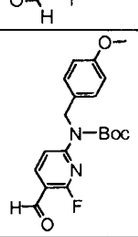
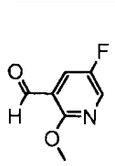
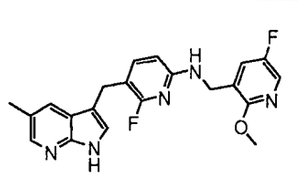
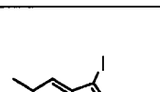
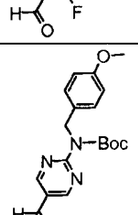
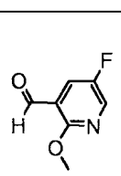
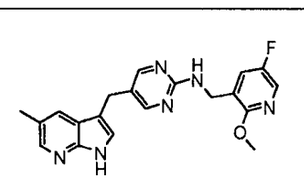
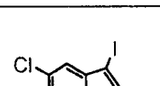
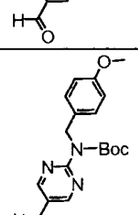
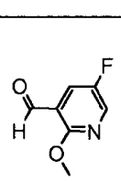
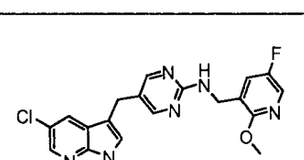
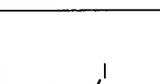
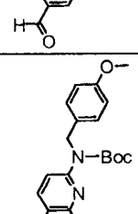
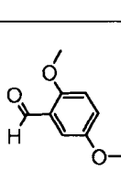
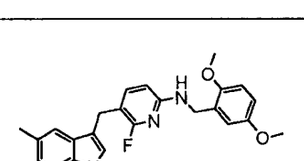
Ethanesulfonic acid (4-fluoro-3-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2199**), and

Ethanesulfonic acid (3-fluoro-5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2202**).

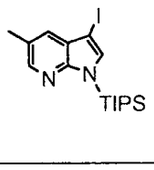
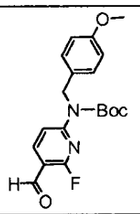
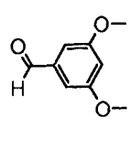
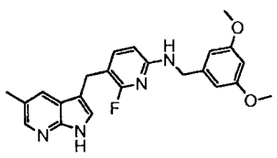
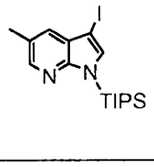
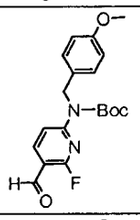
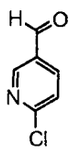
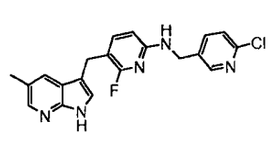
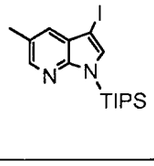
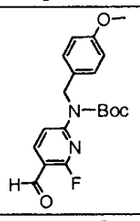
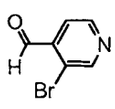
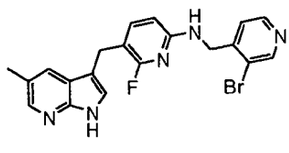
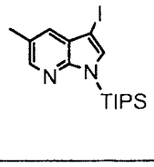
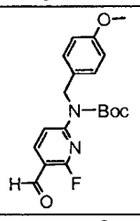
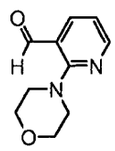
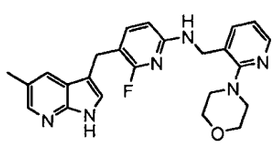
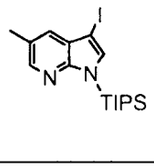
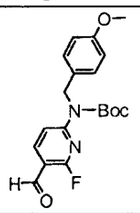
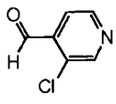
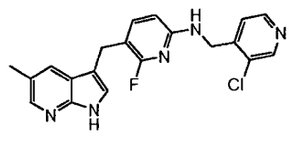
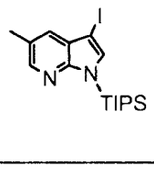
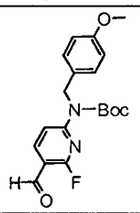
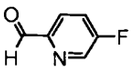
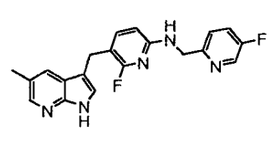
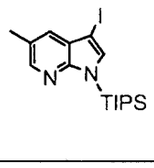
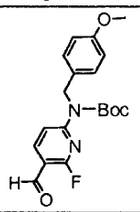
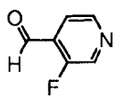
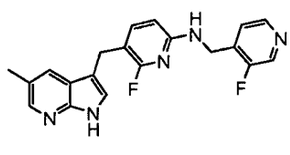
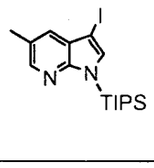
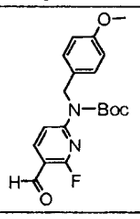
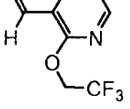
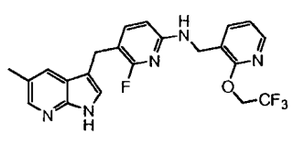
The following table indicates the 1H-pyrrolo[2,3-b]pyridine (column 2) and Boc-protected aldehyde (column 3) used in step 1, and the aldehyde compound (column 4) used in step 3 (or 3a if indicated in column 1) to afford the desired compound (column 5). The compound number is provided in column 1, and the observed mass is in column 6.

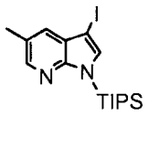
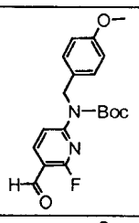
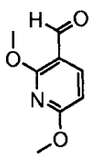
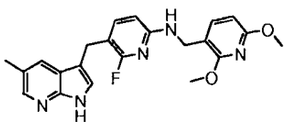
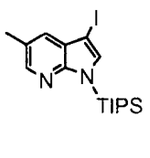
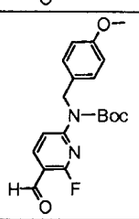
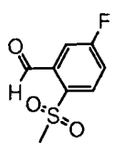
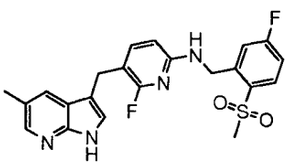
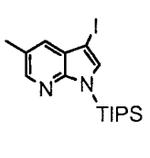
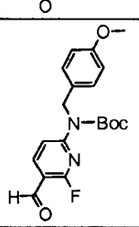
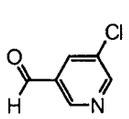
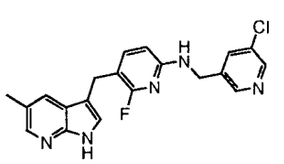
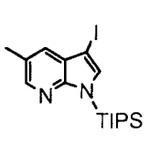
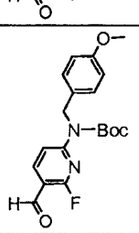
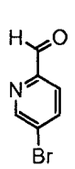
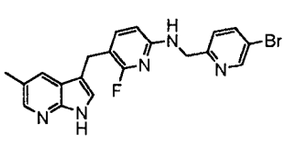
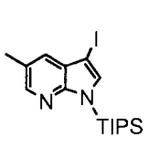
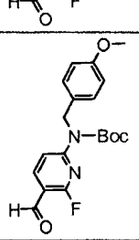
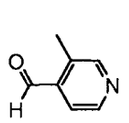
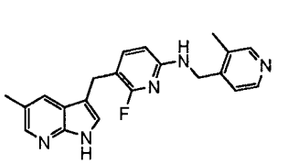
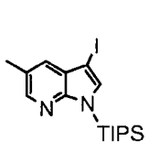
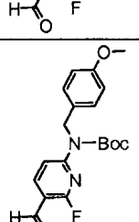
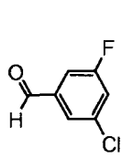
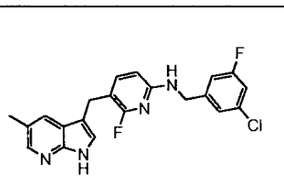
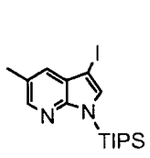
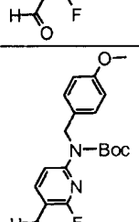
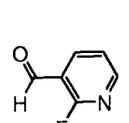
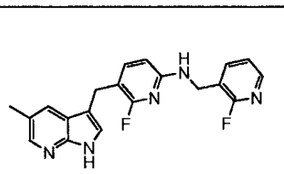
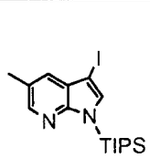
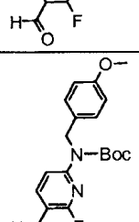
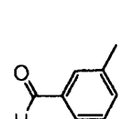
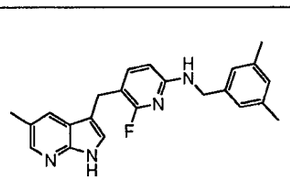
Comp. number	pyrrolo[2,3-b]pyridine	Boc Aldehyde	Step 3 aldehyde	Compound	MS (ESI) $[M+H^+]^+$
P-1569					
P-1570					

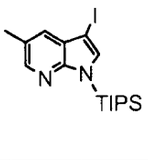
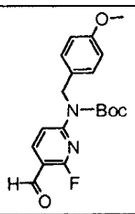
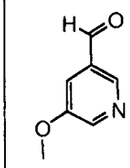
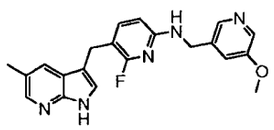
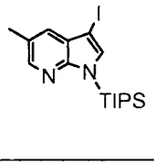
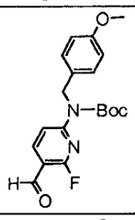
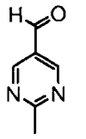
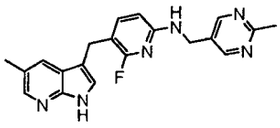
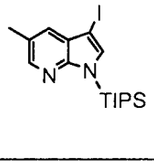
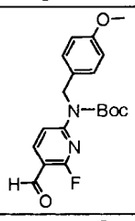
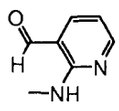
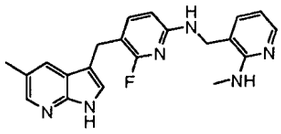
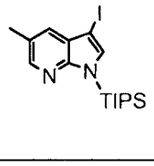
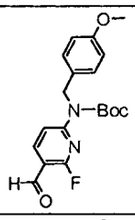
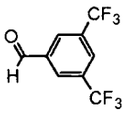
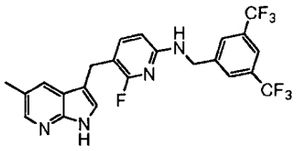
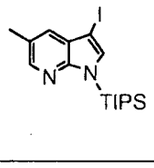
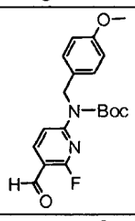
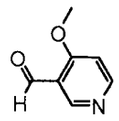
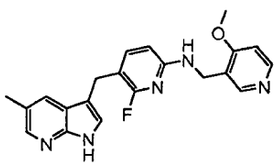
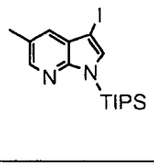
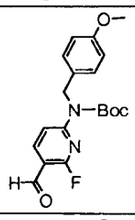
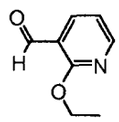
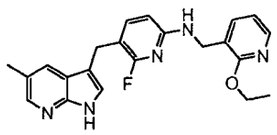
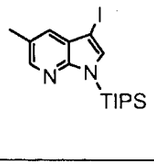
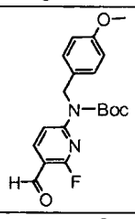
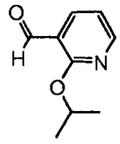
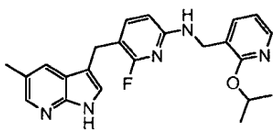
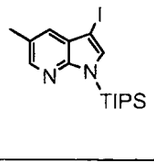
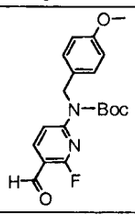
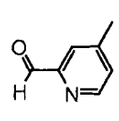
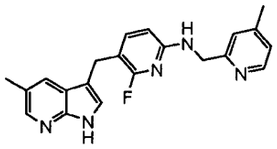
P-1611					
P-1612					
P-1613					
P-1614					
P-1646 (3a)					450.0
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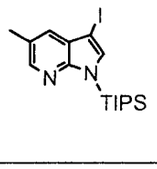
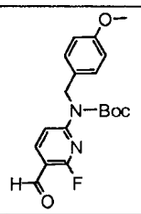
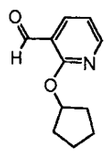
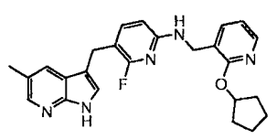
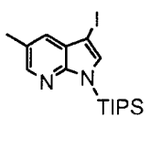
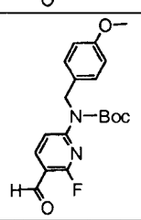
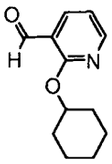
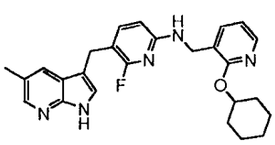
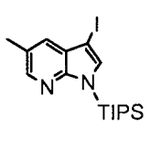
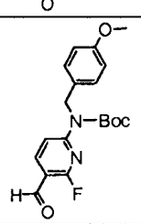
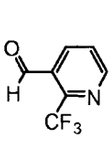
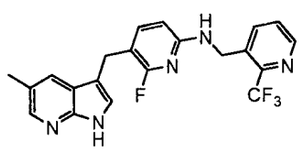
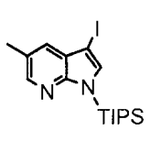
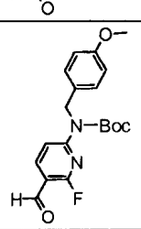
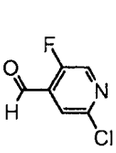
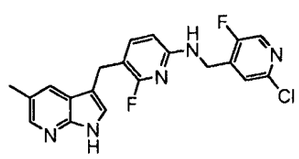
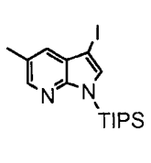
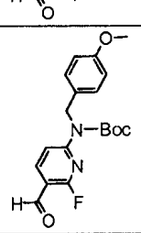
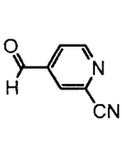
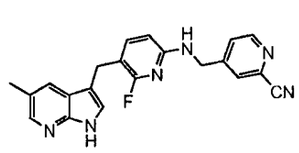
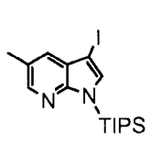
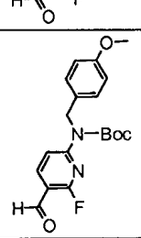
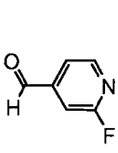
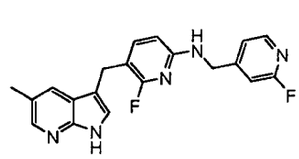
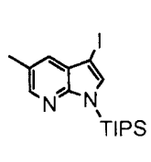
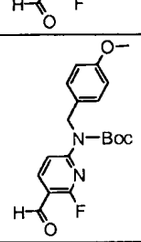
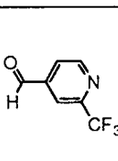
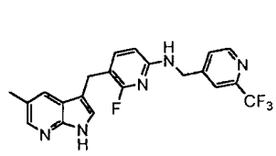
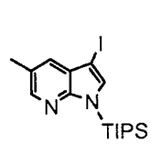
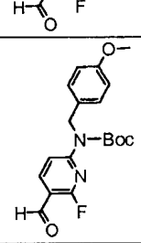
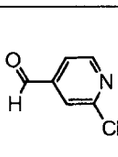
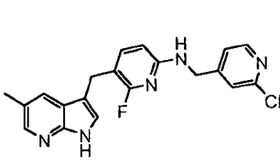
P-1650 (3a)					
P-1651 (3a)					
P-1652 (3a)					
P-1653 (3a)					
P-2049 (3a)					396.0
P-2061					379.0
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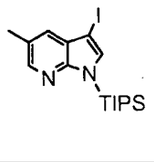
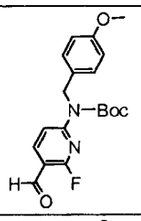
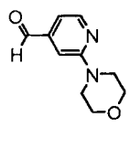
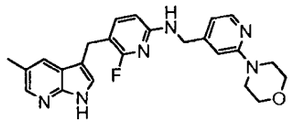
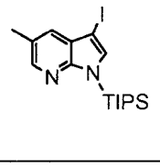
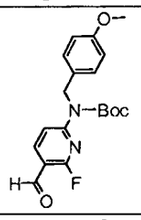
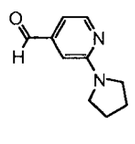
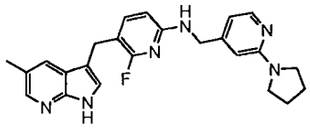
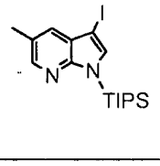
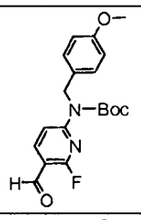
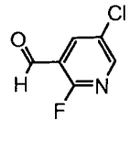
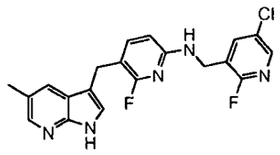
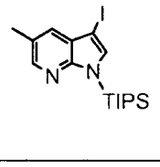
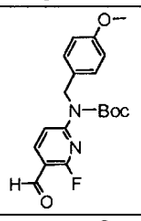
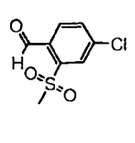
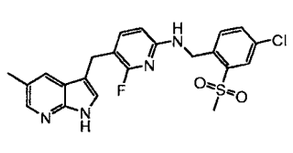
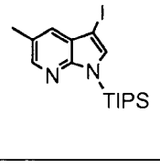
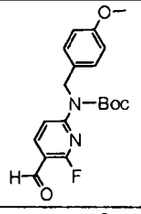
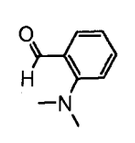
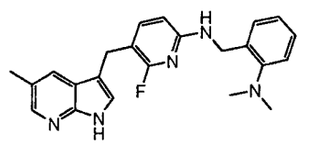
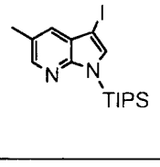
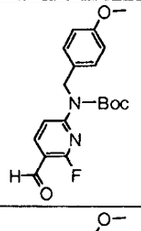
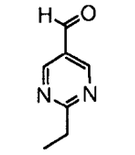
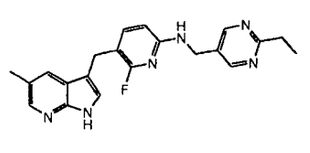
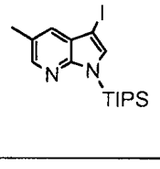
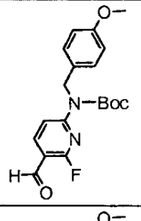
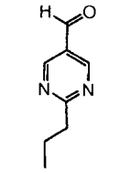
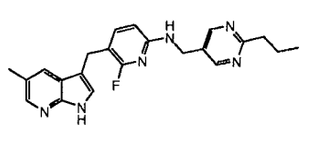
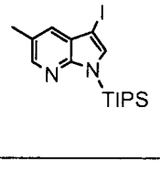
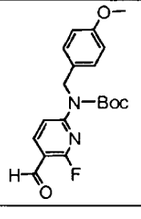
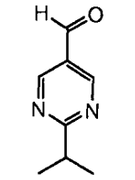
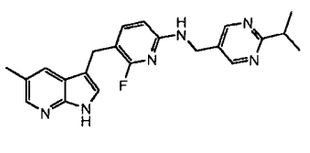
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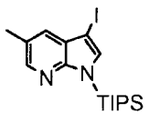
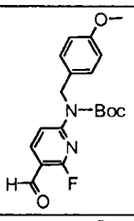
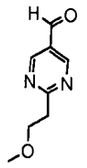
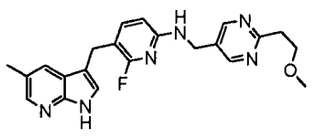
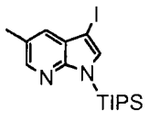
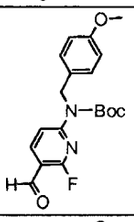
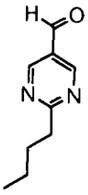
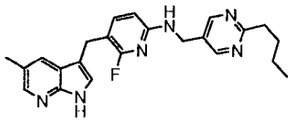
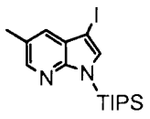
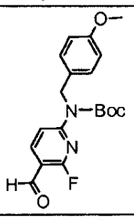
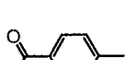
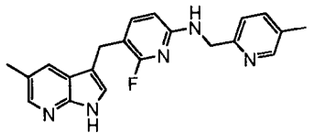
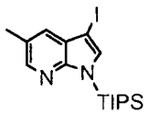
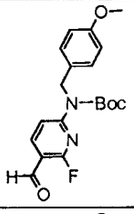
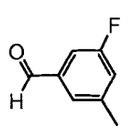
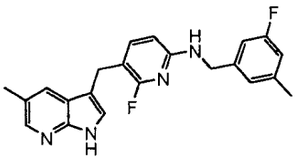
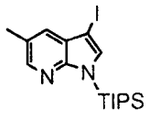
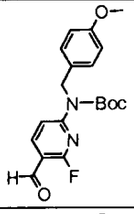
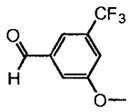
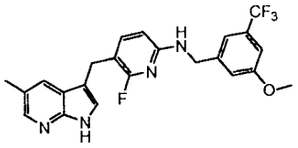
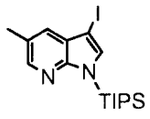
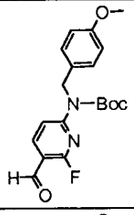
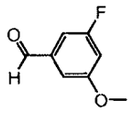
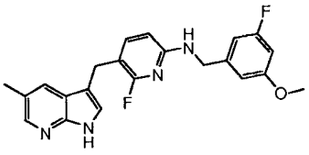
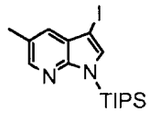
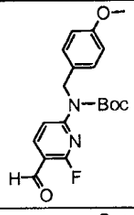
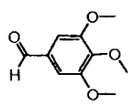
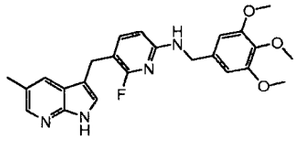
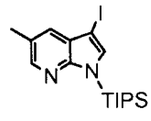
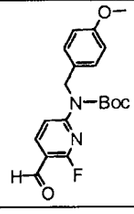
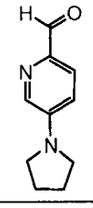
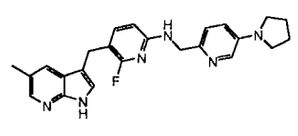
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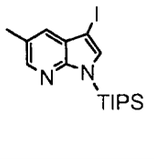
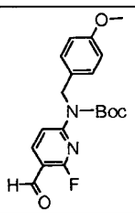
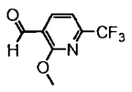
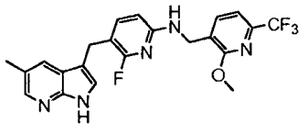
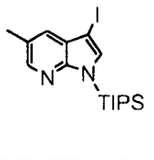
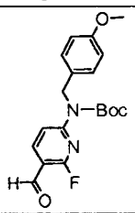
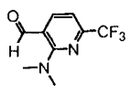
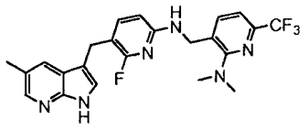
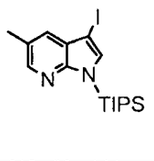
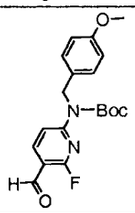
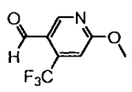
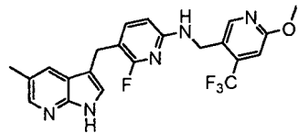
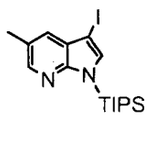
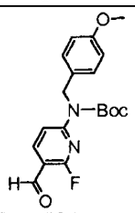
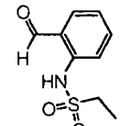
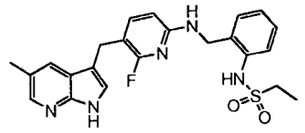
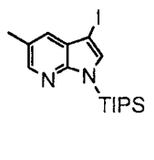
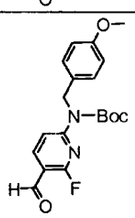
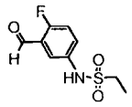
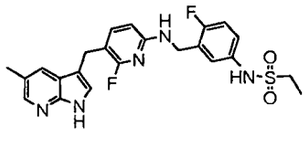
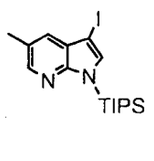
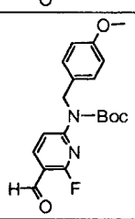
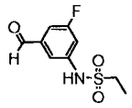
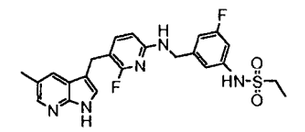
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P-2110					
P-2111					
P-2112					

P-2113					
P-2114					
P-2115					416.3
P-2116					
P-2117					
P-2118					366.3
P-2119					416.3
P-2120					382.3

166

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P-2126					
P-2127					
P-2128					

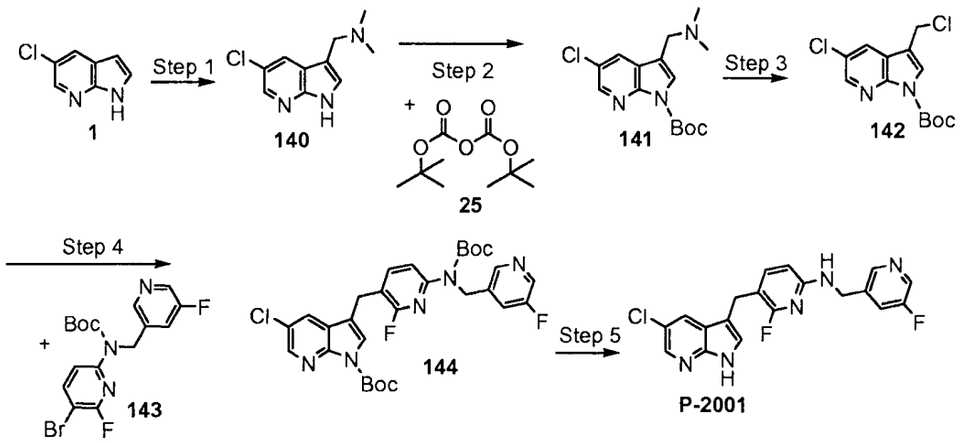
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P-2150					
P-2151					

P-2166 (step 3a)					446.2
P-2167 (step 3a)					459.1
P-2186 (step 3a)					446.4
P-2198 (step 3a)					454.0
P-2199 (step 3a)					472.0
P-2202 (step 3a)					472.1

Example 17: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine P-2001.

[0375] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-2001** was prepared in five steps from 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 17.

Scheme 17



Step 1 – Preparation of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (140):

[0376] To 5-chloro-1H-pyrrolo[2,3-b]pyridine (**1**, 8.00 g, 0.0524 mol) in 250 mL of isopropyl alcohol, dimethylamine hydrochloride (4.79 g, 0.0587 mol) and formaldehyde (1.77 g, 0.0589 mol) were added. The reaction was stirred at room temperature overnight, followed by refluxing for 4 hours. The reaction was concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude compound (**140**, 10.0 g, 91%), that was used directly in the next step.

Step 2: Preparation of 5-chloro-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (141)

[0377] To (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (**140**, 5.00 g, 23.8 mmol,) in 60.0 mL of N,N-dimethylformamide, sodium hydride (1.05 g, 60% in mineral oil, 26.2 mmol) was added. After 10 minutes, di-tert-butyldicarbonate (**25**, 6.24 g, 28.6 mmol) was added and the reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 5% methanol in dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a white solid (**141**, 5.20 g).

Step 3: Preparation of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (142)

[0378] To 5-chloro-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**141**, 4.20 g, 13.6 mmol) in 100 mL of toluene, ethyl chloroformate (1.48 mL, 15.5 mmol) was added under nitrogen. The reaction was stirred at room temperature for 2 hours, then concentrated under vacuum and combined with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide the desired compound (**142**, 1.60 g).

Step 4 – Preparation of 3-{6-[tert-butoxycarbonyl-(5-fluoro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-5-chloro-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (144):

[0379] To (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**143**, 0.600 g, 1.50 mmol) in 10.0 mL of tetrahydrofuran at -25 °C under nitrogen, isopropylmagnesium chloride (0.730 mL, 2.0 M in tetrahydrofuran, 1.46 mmol) was added and the reaction allowed to come to 5 °C over 1 hour. The reaction was then cooled to -35 °C, and CuCN·2LiCl (2.0 mL, 0.75 M in tetrahydrofuran, 1.5 mmol) was added. After 5 minutes, 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**142**, 0.300 g, 0.996 mmol) in 4.0 mL of tetrahydrofuran was added and the reaction allowed to come to room temperature over 1 hour. The reaction was poured into dilute ammonia solution and extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and the solvent removed under vacuum to provide the desired compound (**144**, 130 mg). MS (ESI) $[M+H^+]^+ = 586.2$.

*Step 5 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2001**):*

[0380] To 3-{6-[tert-butoxycarbonyl-(5-fluoro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-5-chloro-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**144**, 0.280 g, 0.478 mmol) in 10.0 mL of dichloromethane, trifluoroacetic acid (1.00 mL, 13.0 mmol) was added and the reaction stirred at room temperature overnight. This was pooled with a separate reaction run similarly and concentrated under vacuum. The resulting material was combined with aqueous potassium carbonate and ethyl acetate and mixed. The aqueous layer was separated and the organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane. Appropriate fractions were combined and the solvent removed under vacuum to provide the desired compound (**P-2001**, 99 mg). MS (ESI) $[M+H^+]^+ = 386.0$.

Preparation of 3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204)**

[0381] To 5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine (125 mg, 0.27 mmol) was added 2 mL of N,N-dimethylacetamide. The mixture suspension was degassed by bubbling with argon. To this suspension was added Zinc (5 mg, 0.08 mmol), 11,1'-Bis(diphenylphosphino)ferrocene (6 mg, 0.01 mmol), Zinc Cyanide (0.01 ml, 0.19 mmol), and Tris(dibenzylideneacetone)dipalladium (0) (7 mg, 0.01 mmol) at room temperature under argon. The mixture was heated to 120 °C for 2 hrs and cooled to room temperature. The reaction mixture was extracted with ethyl acetate and water (+saturated sodium chloride). The

organic layer was washed with water and brine, dried by $MgSO_4$. The volatiles were removed under vacuum. The residue was suspended in acetonitrile and sonicated for 45 mins. The precipitate was collected by filtration and washed with acetonitrile. A tan solid was obtained (98 mg, 88.8% yield). LC-MS showed one major peak with 98.6 % purity. The structure of the product is confirmed by H^1-NMR(DMSO-d6). MS (ESI) $[M+H]^+ = 406.9$.

[0382] Additional compounds are prepared following the protocol of Scheme 17, where 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. Compounds are prepared optionally replacing 5-chloro-1H-pyrrolo[2,3-b]pyridine **1** with a suitable 5-substituted-1H-pyrrolo[2,3-b]pyridine in step 1 and optionally replacing (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **143** with a suitable N-protected bromo (or other suitable halo) compound in step 4. The following compounds are made using this procedure. Compounds in the following table were characterized by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.

3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1654**),

3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1655**),

3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1656**),

3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1657**),

3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1658**),

3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1659**),

3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-1660**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2027**),

[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2028**),

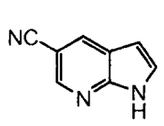
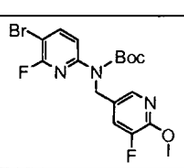
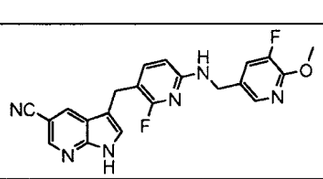
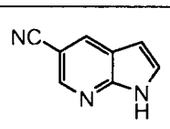
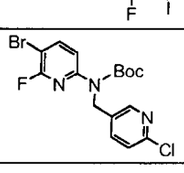
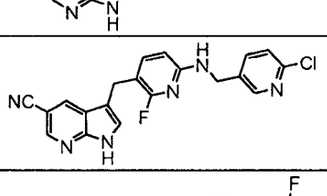
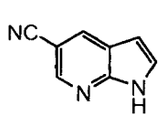
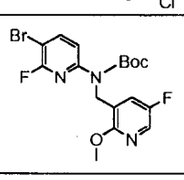
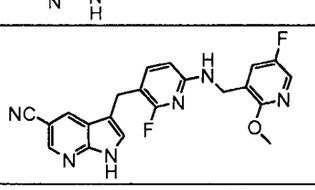
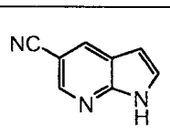
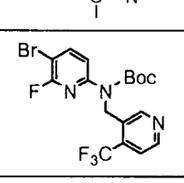
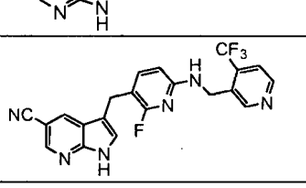
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),

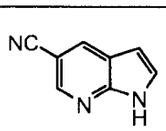
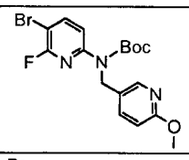
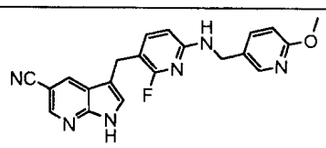
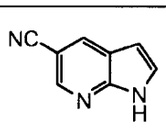
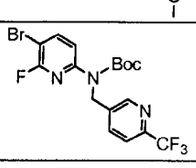
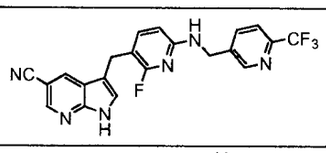
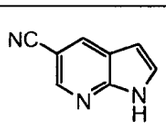
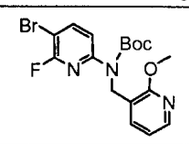
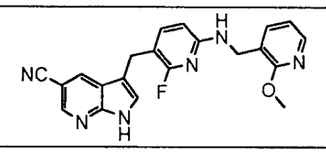
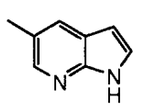
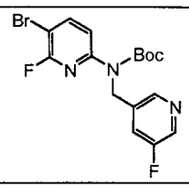
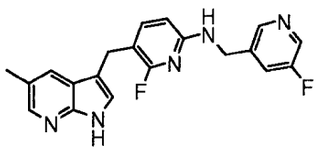
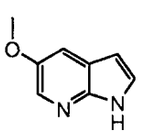
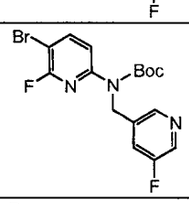
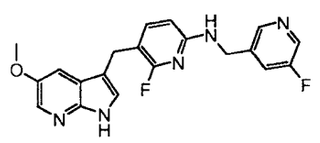
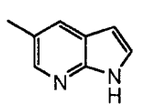
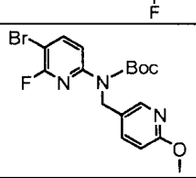
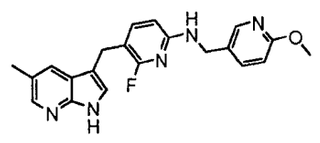
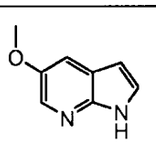
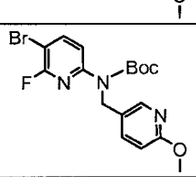
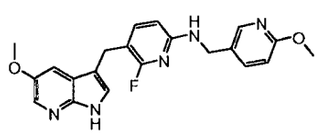
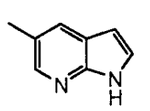
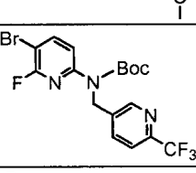
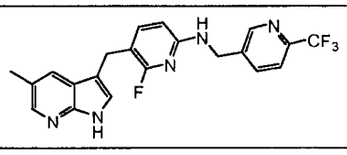
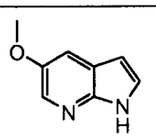
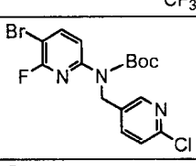
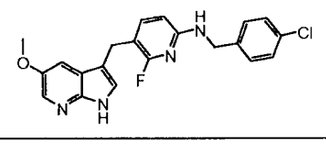
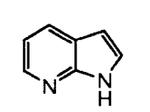
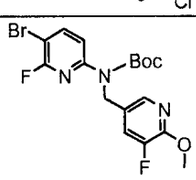
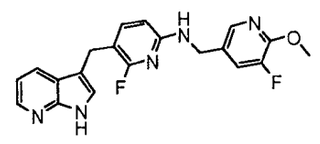
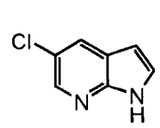
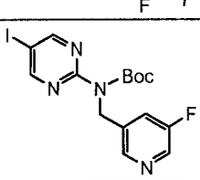
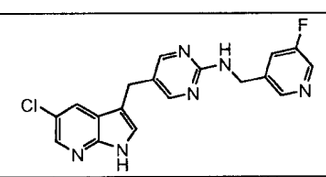
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-

ylmethyl)-amine (**P-2030**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2041**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2176**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),** and

6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**.

The following table indicates the 1H-pyrrolo[2,3-b]pyridine compound (column 2) used in step 1 and halogen substituted compound (column 3) used in step 4 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

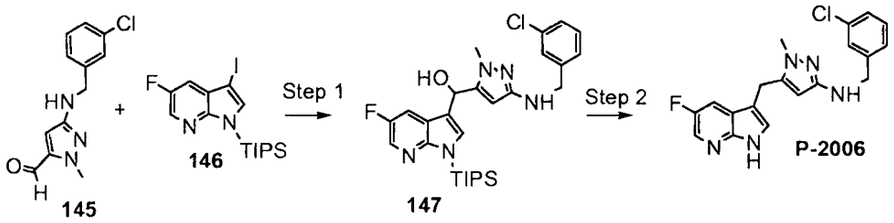
Comp. number	1H-pyrrolo[2,3-b]pyridine	Halogen compound	Compound structure	MS (ESI) $[M+H^+]^+$
P-1654				
P-1655				
P-1656				407.2
P-1657				

P-1658				
P-1659				
P-1660				
P-2027				366.0
P-2028				381.9
P-2029				378.0
P-2030				394.2
P-2031				381.9
P-2032				396.9
P-2041				
P-2176				369.1

Example 18: Synthesis of (3-chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine P-2006.

[0383] (3-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine **P-2006** was prepared in two steps from 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carbaldehyde **145** and 5-fluoro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **146** as shown in Scheme 18.

Scheme 18



Step 1 – Preparation of [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-fluoro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (147):

[0384] 5-Fluoro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**146**, 0.33 g, 0.79 mmol) and 1.5 mL of tetrahydrofuran were combined in a round bottom flask and cooled to -20 °C. Isopropylmagnesium chloride (400 µL, 2.0 M in tetrahydrofuran, 0.8 mmol) was added dropwise and the reaction stirred and brought to -5 °C. The reaction was cooled to -20 °C and 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carbaldehyde (**145**, 0.090 g, 0.36 mmol) in tetrahydrofuran was added and the reaction stirred and brought to 0 °C. The reaction was concentrated under vacuum, diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, then brine. The organic layer was separated and dried over sodium sulfate, filtered and the filtrate purified by silica gel flash column chromatography eluting with a gradient of 5-80% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+$ = 542.7, 543.95.

*Step 2 – Preparation of (3-chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine (**P-2006**):*

[0385] To [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-fluoro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**147**, 0.070 g, 0.13 mmol) in 4 mL of dichloromethane, triethylsilane (0.210 mL, 1.31 mmol) and trifluoroacetic acid (0.100 mL, 1.30 mmol) were added and the reaction stirred overnight at room temperature. The reaction was concentrated under vacuum, then ethyl acetate was added, then washed with 1M aqueous potassium carbonate, then brine. The organic layer was dried over sodium sulfate, filtered and the filtrate purified by silica gel flash column chromatography eluting with a gradient of 2-20% methanol in dichloromethane. Appropriate

fractions were combined and concentrated under vacuum and the resulting solid washed with ethyl acetate in hexane to provide the desired compound.

[0386] The following compounds are prepared following the protocol of Scheme 18, where 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. The following compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

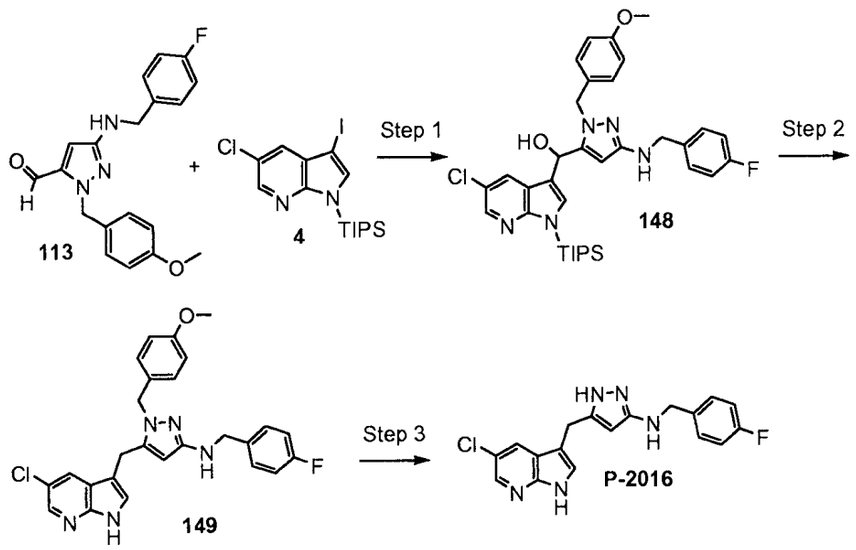
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),** and

6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)**.

Example 19: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine P-2016.

[0387] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-2016** was prepared in three steps from 5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carbaldehyde **113** and 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **4** as shown in Scheme 19.

Scheme 19



*Step 1 – Preparation of (5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-[5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-methanol (**148**):*

[0388] In a round bottom flask, 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**4**, 1.7 g, 3.9 mmol) was combined with 1.3 mL of tetrahydrofuran and cooled to -20 °C. Isopropylmagnesium chloride (2.0 mL, 2 M in tetrahydrofuran, 4.0 mmol) was added dropwise and the reaction stirred at -5 °C. The reaction was cooled to -20 °C and 5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazole-3-carbaldehyde (**113**, 0.622 g, 1.83 mmol) in 2 mL of tetrahydrofuran was added and the reaction stirred at 0 °C. The reaction was concentrated under vacuum, diluted with ethyl acetate and washed with sodium bicarbonate and brine. The organic layer was dried with sodium sulfate and purified by silica gel column chromatography, eluting with 5-80% ethyl acetate in hexanes. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound. MS (ESI) $[M+H^+]^+ = 648.38$ and 649.74.

*Step 2 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-(4-methoxy-benzyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**149**):*

[0389] In a quartz vial, (5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-[5-(4-fluoro-benzylamino)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-methanol (**148**, 0.328 g, 0.506 mmol) was combined with 20 mL of dichloromethane, triethylsilane (0.4 mL, 2.0 mmol) was added, followed by trifluoroacetic acid (0.2 mL, 2.0 mmol). The reaction was stirred overnight at room temperature, then concentrated under vacuum and ethyl acetate was added. This was washed with 1 M aqueous potassium carbonate and brine, dried with sodium sulfate, and purified by silica gel column chromatography, eluting with 2-20% methanol in dichloromethane. Appropriate fractions were combined and concentrated under vacuum, and the solid further washed with ethyl acetate and hexane to provide the desired compound. ^{1}H NMR was consistent with compound structure.

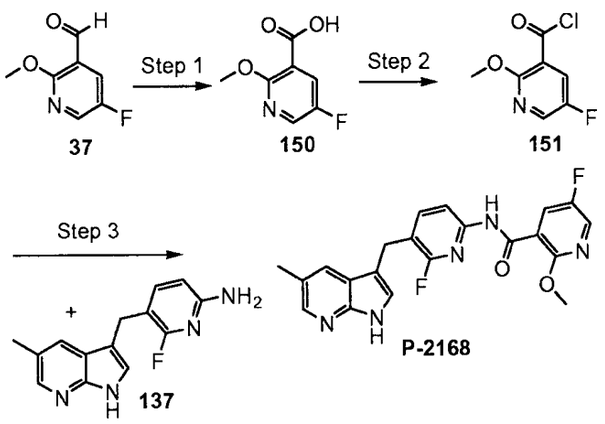
*Step 3 – Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-2016**):*

[0390] Into a round bottom flask, [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-(4-methoxy-benzyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**149**, 0.060 g, 0.13 mmol) was dissolved in 5 mL of trifluoroacetic acid (60 mmol) and the reaction was heated at 70 °C overnight. The reaction was cooled to room temperature, then concentrated under vacuum and ethyl acetate was added. This was washed with 1 M aqueous potassium carbonate and brine, dried with sodium sulfate and purified by silica gel column chromatography, eluting with 2-20% methanol in dichloromethane. Appropriate fractions were combined and concentrated under vacuum, and the solid further washed with ethyl acetate and hexane to provide the desired compound. ^{1}H NMR was consistent with compound structure. MS (ESI) $[M+H^+]^+ = 356.85$.

Example 20: Synthesis of 5-fluoro-N-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-2-methoxy-nicotinamide P-2168.

[0391] 5-Fluoro-N-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-2-methoxy-nicotinamide **P-2168** was prepared in three steps from 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37** as shown in Scheme 20.

Scheme 20



Step 2 – Preparation of 5-fluoro-2-methoxy-nicotinic acid (150):

[0392] In a round bottom flask, 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (**37**, 0.500 g, 3.22 mmol) was combined with sodium chlorite (0.6734 g, 5.957 mmol), 30 mL of 1,4-dioxane, 10 mL of water, and sulfamic acid (2.39 g, 24.6 mmol). The reaction mixture was stirred at room temperature for 5 minutes, then poured into 100 mL of water and extracted with 100 mL of ethyl acetate. The organic layer was washed with water, brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound (**150**, 512 mg), used in the next step without further purification.

Step 2 – Preparation of 5-fluoro-2-methoxy-nicotinoyl chloride (151):

[0393] In a round bottom flask, 5-fluoro-2-methoxy-nicotinic acid (**150**, 250 mg, 1.46 mmol) was combined with thionyl chloride (3.00 mL, 41.1 mmol) and the suspension was stirred at room temperature for 3 hours. The reaction was concentrated to dryness under vacuum to provide the desired compound, used in the next step without further purification.

*Step 3 – Preparation of 5-fluoro-N-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-2-methoxy-nicotinamide (**P-2168**):*

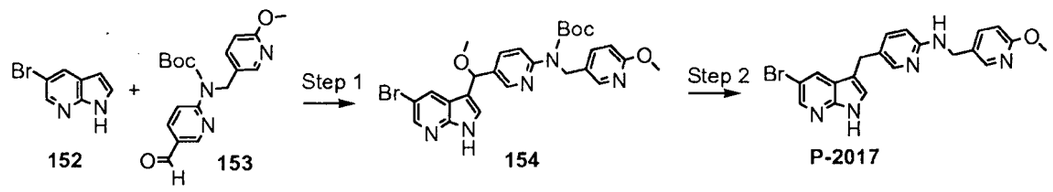
[0394] In a reaction flask, 6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**137**, 100 mg, 0.3902 mmol) was combined with 5-fluoro-2-methoxy-nicotinoyl chloride (**151**, 81.37 mg, 0.4292 mmol), 3.00 mL of tetrahydrofuran, and pyridine (0.06312 mL, 0.7804 mmol). The reaction was stirred at room temperature overnight, then poured into aqueous 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography, eluting with 1-5% methanol in dichloromethane. Appropriate fractions were

combined and concentrated under vacuum to provide the desired compound (**P-2168**, 100 mg). MS (ESI) $[M+H^+]^+ = 409.9$.

Example 21: Synthesis of [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine P-2017.

[0395] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **P-2017** was prepared in two steps from 5-bromo-1H-pyrrolo[2,3-b]pyridine **152** and (5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **153** as shown in Scheme 21.

Scheme 21



*Step 1 – Preparation {5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methoxy-methyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**154**):*

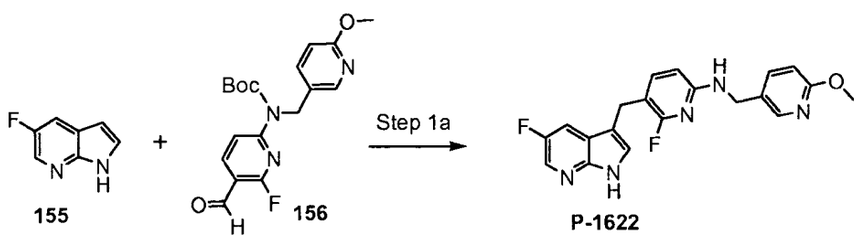
[0396] To 5-bromo-1H-pyrrolo[2,3-b]pyridine (**152**, 0.622 g, 3.16 mmol) in 50.0 mL of methanol under nitrogen, (5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**153**, 1.05 g, 3.06 mmol) and potassium hydroxide (1.50 g, 26.7 mmol) were added and the reaction stirred at room temperature overnight. The reaction was poured into water, extracted with ethyl acetate, the organic layer dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with a gradient of 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**154**, 0.35 g). {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester was also formed in this procedure and could be isolated and reacted similarly to the following step to form the desired product.

*Step 2 – Preparation of [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2017**):*

[0397] To {5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methoxy-methyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**154**, 0.35 g, 0.63 mmol) in 20.0 mL of acetonitrile, triethylsilane (1.0 mL, 6.3 mmol) and trifluoroacetic acid (0.50 mL, 6.5 mmol) were added and the reaction stirred at 80 °C for 4 hours. The reaction was concentrated under vacuum and combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was

filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**P-2017**, 165.1 mg). MS (ESI) $[M+H^+]^+ = 423.8, 425.8$.

[0398] [6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **P-1622** is prepared similarly to Scheme 21, reacting in a single step 1a as follows.



*Step 1a – Preparation of [6-fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1622**):*

[0399] In a round bottom flask, 5-fluoro-1H-pyrrolo[2,3-b]pyridine (**155**, 0.115 g, 0.845 mmol) was combined with (6-fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**156**, 0.397 g, 1.10 mmol), 2.60 mL of acetonitrile, trifluoroacetic acid (0.325 mL, 4.22 mmol) and triethylsilane (0.810 mL, 5.07 mmol) and the reaction was heated to reflux for 3 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate in hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**P-1622**, 28 mg). MS (ESI) $[M+H^+]^+ = 382.1$.

[0400] Additional compounds are prepared following the protocol of Scheme 21 (or single step 1a), where 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. Compounds are prepared optionally using a suitable 1H-pyrrolo[2,3-b]pyridine in place of 5-bromo-1H-pyrrolo[2,3-b]pyridine **152** and optionally using a suitable aldehyde in place of (5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **153** in step 1. Further, either or both of the methoxy or hydroxy intermediate formed in step 1 are reacted in the second step. The following compounds are made using this procedure. Compounds in the following table were characterized by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-

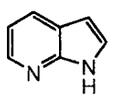
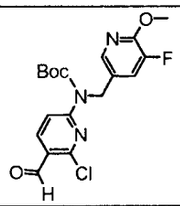
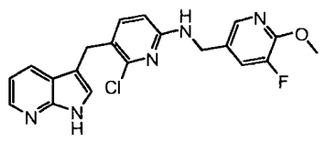
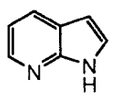
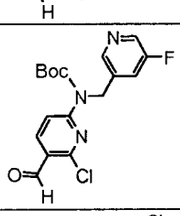
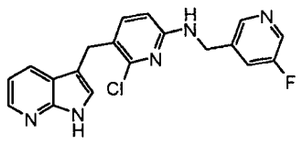
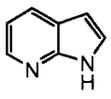
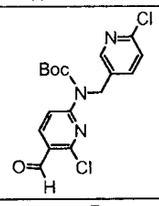
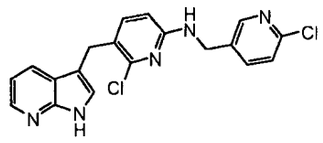
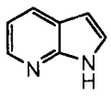
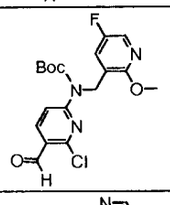
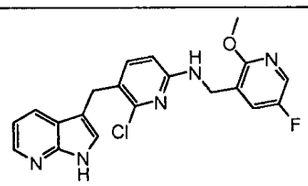
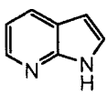
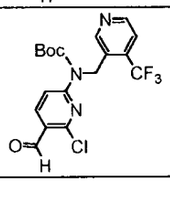
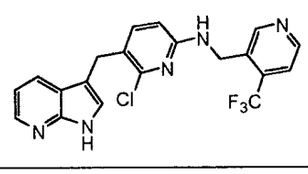
ylmethyl)-amine (**P-1506**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1507**),
(6-Chloro-pyridin-3-ylmethyl)-[6-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1508**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1509**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1510**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1511**),
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1512**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1528**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1529**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1530**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1531**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1583**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1584**),
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(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1586**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1587**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1588**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1589**),
[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1590**),

[6-Chloro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1591**),
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[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1626**),
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(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1638**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1639**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1640**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1641**),
(4-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1642**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-

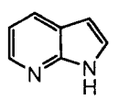
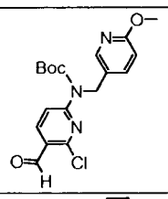
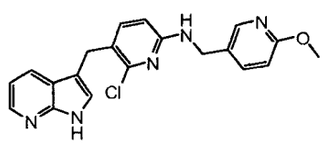
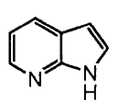
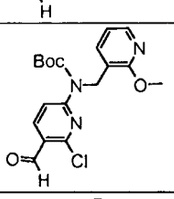
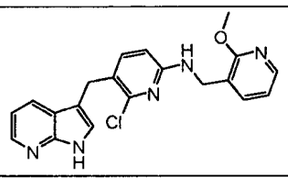
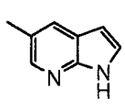
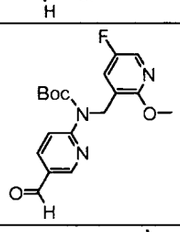
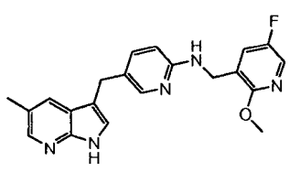
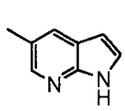
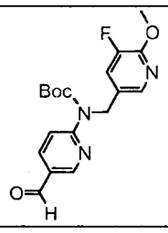
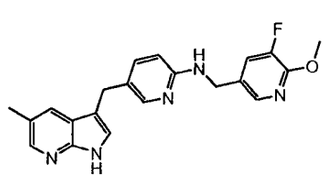
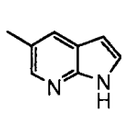
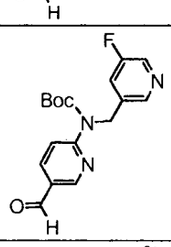
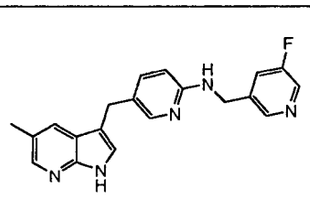
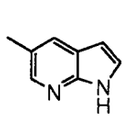
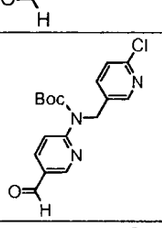
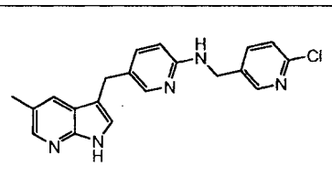
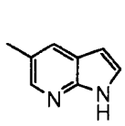
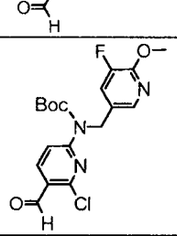
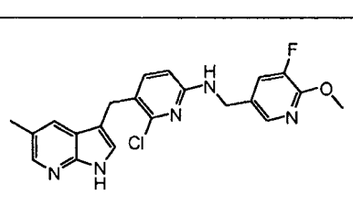
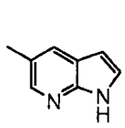
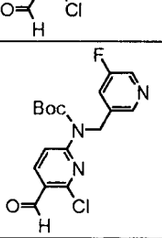
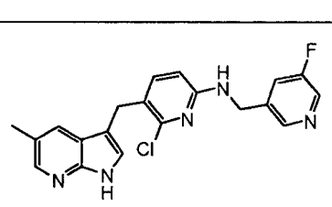
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(6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1644**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1645**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1661**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1662**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1663**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1664**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1665**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1666**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1667**),
[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1668**),
3-{6-[(5-Fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1719**),
3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1720**),
3-{6-[(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1721**),
3-{6-[(4-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1722**),
3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1723**),
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1724**),
3-{6-[(2-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1725**),
3-{6-[(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**P-1726**),

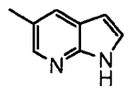
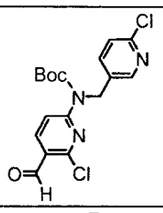
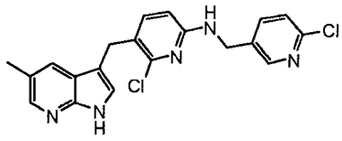
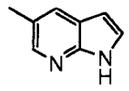
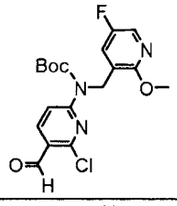
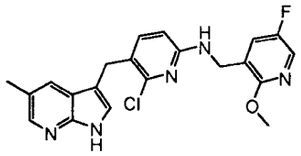
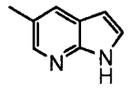
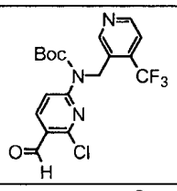
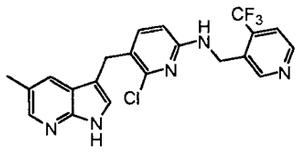
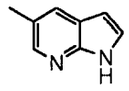
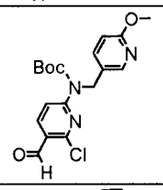
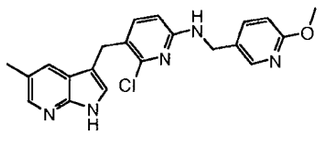
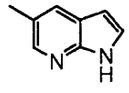
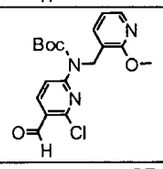
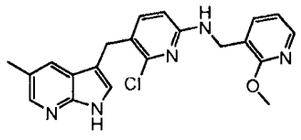
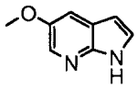
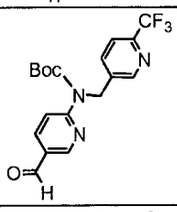
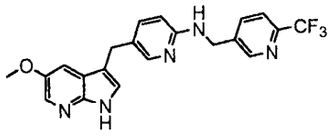
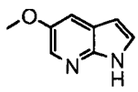
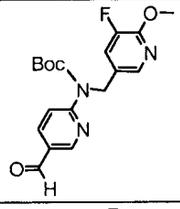
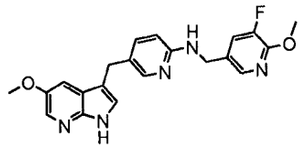
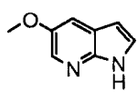
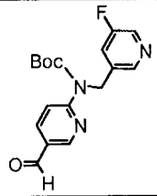
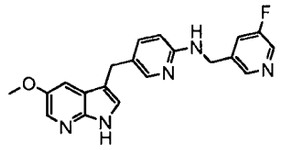
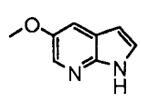
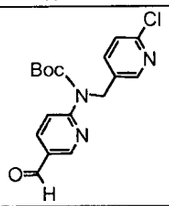
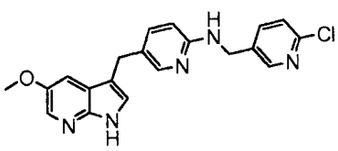
[5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2018**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2023**),
(2-Fluoro-benzyl)-[5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2033**), and
[5-(4-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2170**).

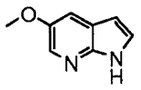
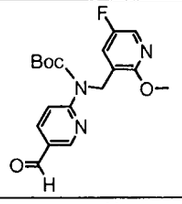
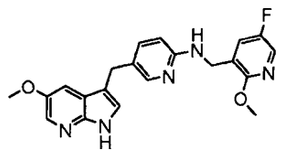
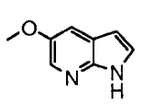
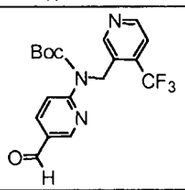
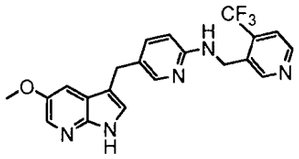
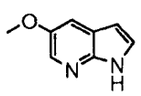
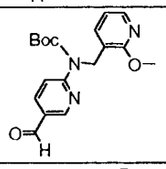
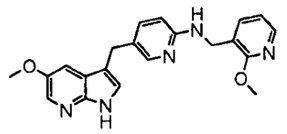
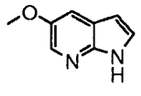
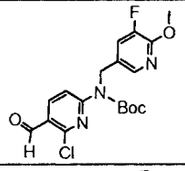
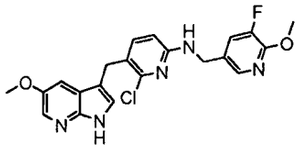
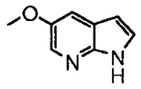
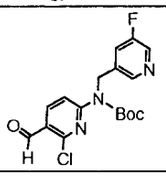
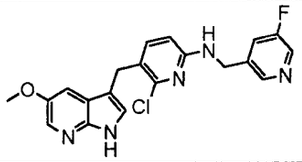
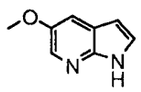
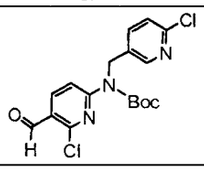
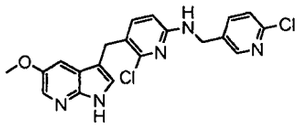
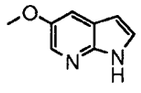
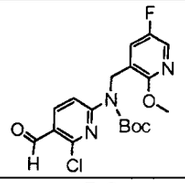
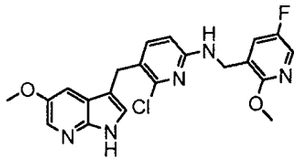
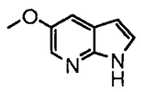
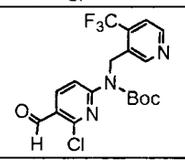
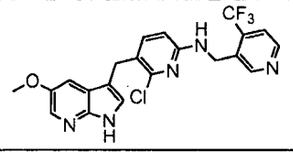
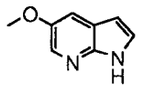
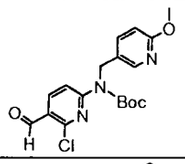
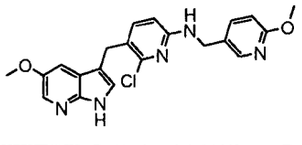
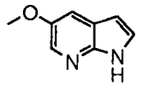
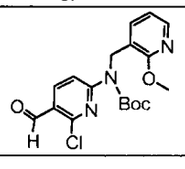
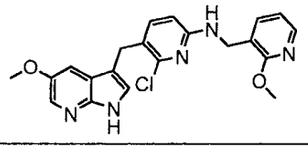
The following table indicates the 1H-pyrrolo[2,3-b]pyridine compound (column 2) and aldehyde compound (column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

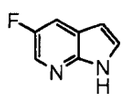
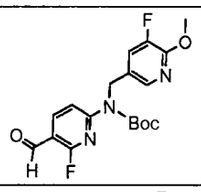
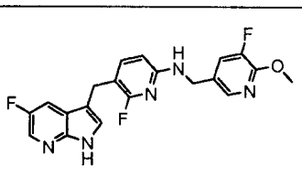
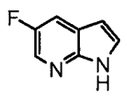
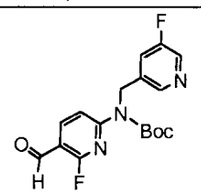
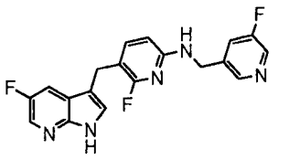
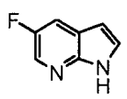
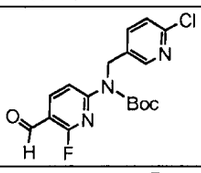
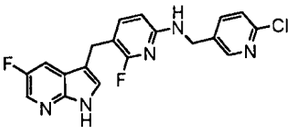
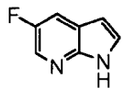
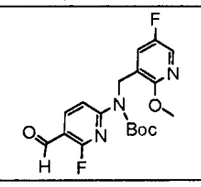
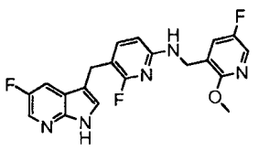
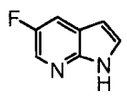
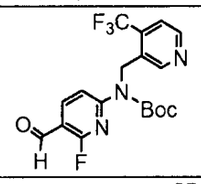
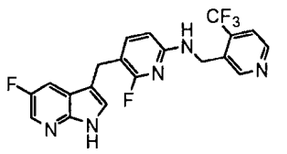
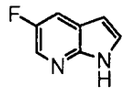
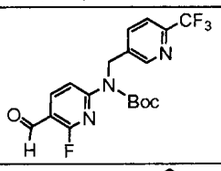
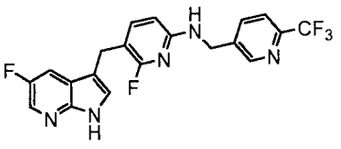
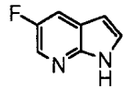
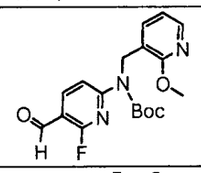
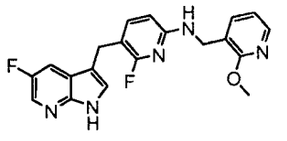
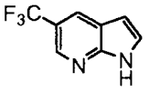
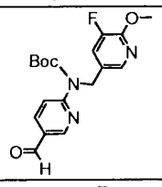
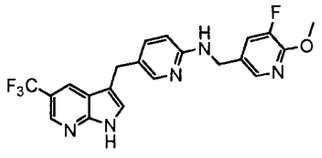
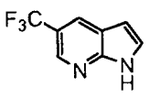
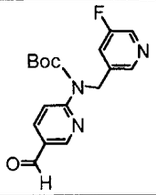
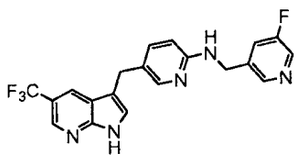
Comp. number	1H-pyrrolo[2,3-b]pyridine	Aldehyde	Compound structure	MS (ESI) $[M+H^+]^+$
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P-1507				
P-1508				
P-1509				
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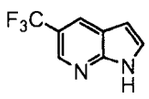
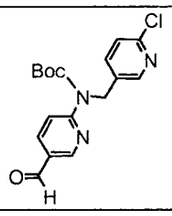
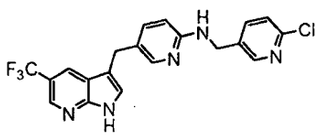
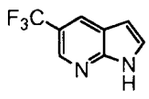
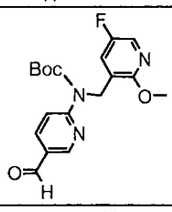
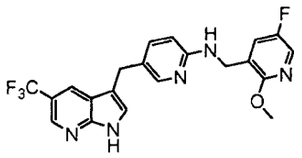
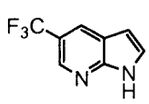
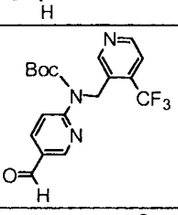
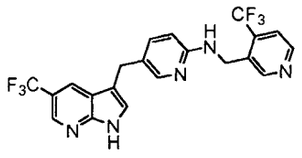
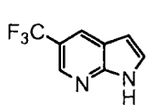
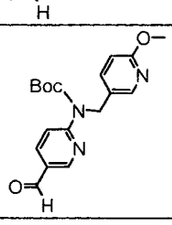
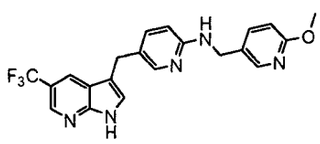
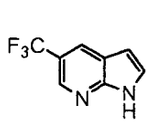
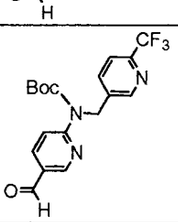
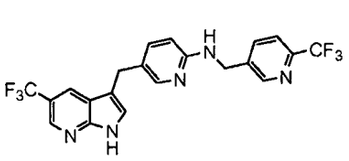
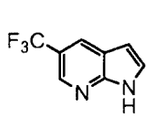
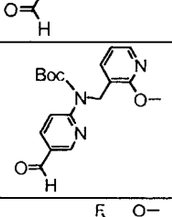
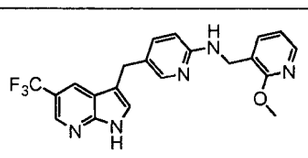
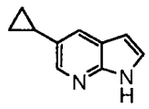
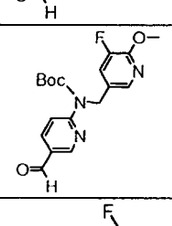
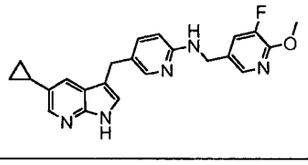
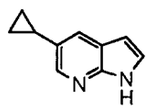
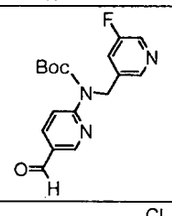
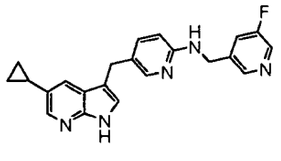
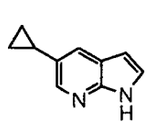
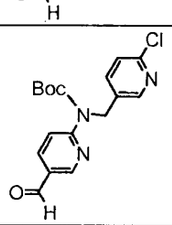
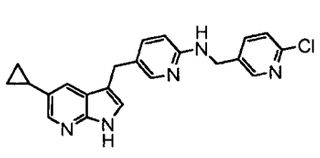
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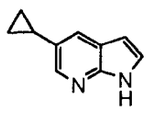
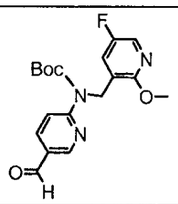
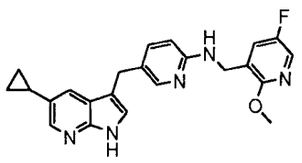
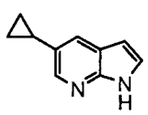
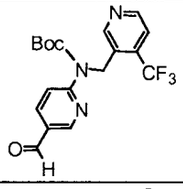
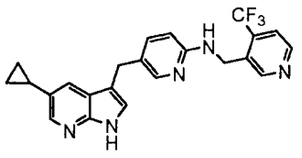
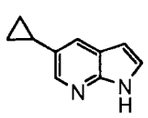
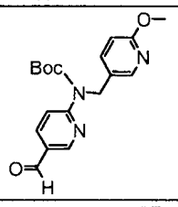
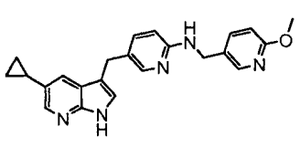
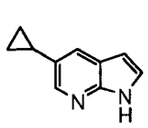
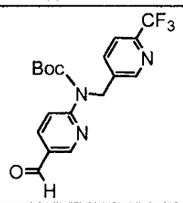
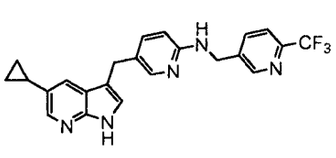
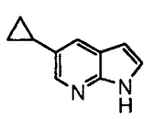
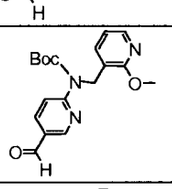
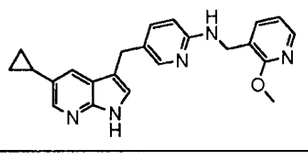
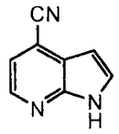
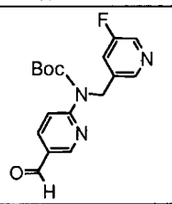
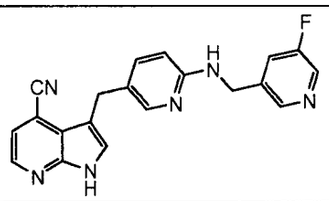
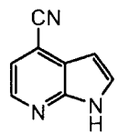
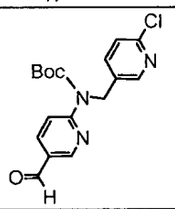
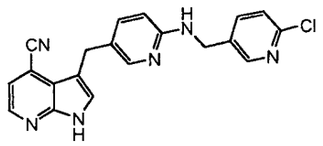
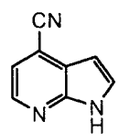
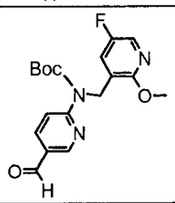
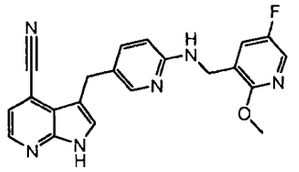
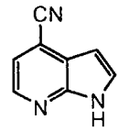
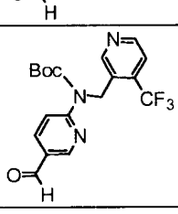
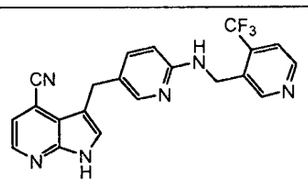
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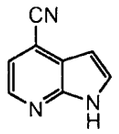
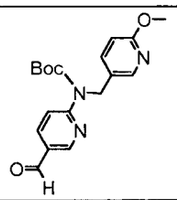
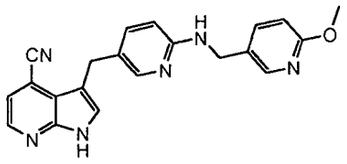
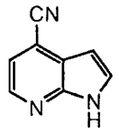
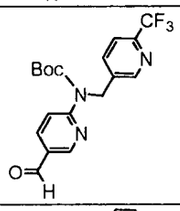
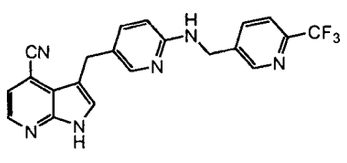
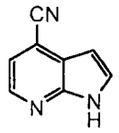
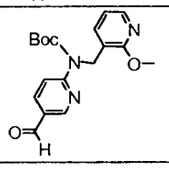
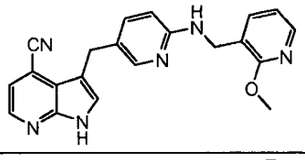
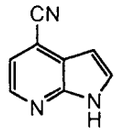
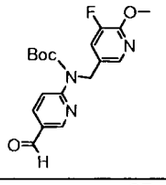
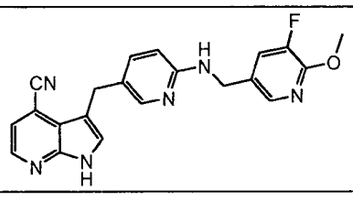
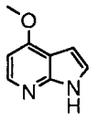
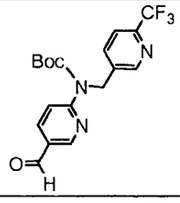
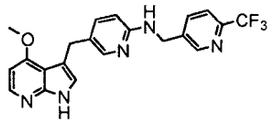
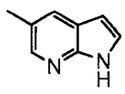
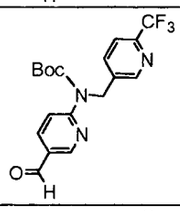
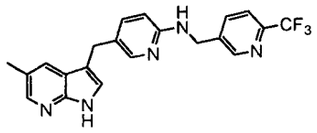
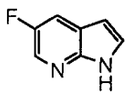
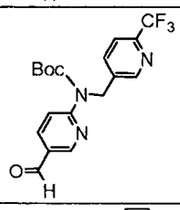
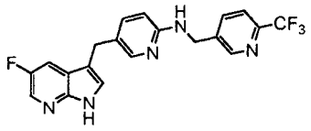
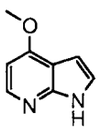
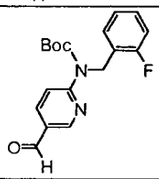
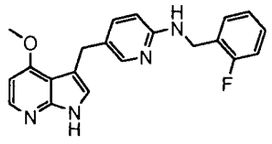
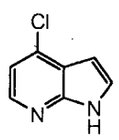
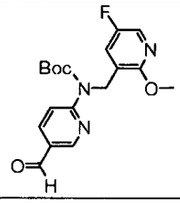
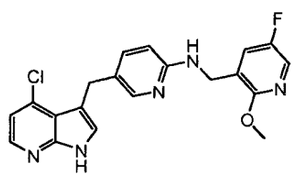
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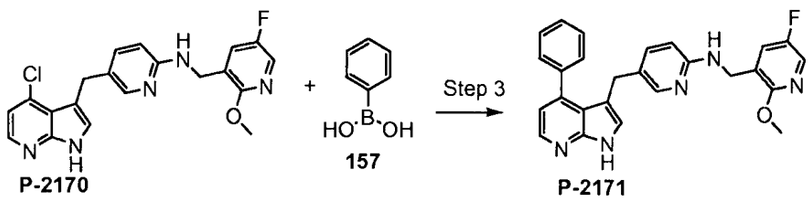
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P-1642				
P-1643				
P-1644				452.0
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P-1721				
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P-1723				
P-1724				
P-1725				
P-1726				
P-2018				
P-2019				398.4
P-2023				
P-2033				363.5
P-2170				

[0401] [5-(4-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine **P-2170** is further reacted to provide (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(4-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-2171** following the protocol of the following step 3.



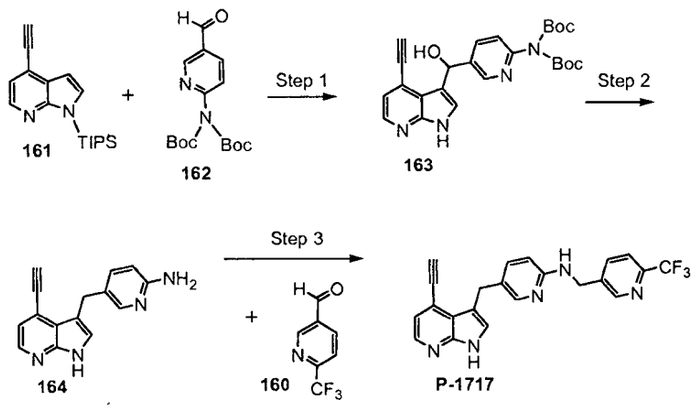
*Step 3 – Preparation of 5-fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(4-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2171**):*

[0402] [5-(4-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (P-2170, 1 equivalent), phenyl boronic acid (**157**, 1.5 equivalents) and tetrakis(triphenylposphine)palladium(0) (catalyst) are combined with 0.33 mL of aqueous potassium carbonate (1.00 M, 3 equivalents) and 0.34 mL of acetonitrile. The resulting mixture is heated in a microwave at 120 °C for 10 minutes, followed by 130 °C for 55 minutes. The mixture is diluted with ethyl acetate and water and the aqueous layer is separated and extracted with ethyl acetate. The organic layers are combined and 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 methanol and dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound.

Example 22: Synthesis of [5-(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine P-1717.

[0403] [5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-1717** was prepared in three steps from 4-ethynyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **161** and (5-formyl-pyridin-2-yl)-di-carbamic acid tert-butyl ester **162** as shown in Scheme 22.

Scheme 22



*Step 1 – Preparation of {5-[(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-di-carbamic acid tert-butyl ester (**163**):*

[0404] In a round bottom flask, 4-ethynyl-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**161**, 0.321 g, 1.08 mmol) was combined with (5-formyl-pyridin-2-yl)-di-carbamic acid tert-butyl ester (**162**, 0.416 g, 1.29 mmol), 2.1 mL of methanol, and potassium hydroxide (0.302 g, 5.38 mmol) and stirred at room temperature for 24 hours. The reaction was neutralized with aqueous 0.1 N hydrochloric acid, then extracted 3x with ethyl acetate. The combined organic layer was washed with brine, then dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with methanol and dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**163**, 229 mg). MS (ESI) $[M-H^+]^-$ = 337.2.

*Step 2 – Preparation of 5-(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**164**):*

[0405] In a round bottom flask, {5-[(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-di-carbamic acid tert-butyl ester (**163**, 0.225 g, 0.484 mmol) was combined with trifluoroacetic acid (0.70 mL, 9.1 mmol), triethylsilane (1.8 mL, 11.0 mmol) and 5.2 mL of acetonitrile and the reaction was heated to reflux for 6 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with methanol and dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**164**, 57 mg). MS (ESI) $[M+H^+]^+$ = 248.9.

*Step 3 – Preparation of [5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1717**):*

[0406] In a round bottom flask, 5-(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**164**, 0.055 g, 0.22 mmol) was combined with 6-trifluoromethyl-pyridine-3-carbaldehyde (**160**, 50.4 mg, 0.288 mmol), 0.682 mL of acetonitrile, trifluoroacetic acid (0.0853 mL, 1.11 mmol),

and triethylsilane (0.212 mL, 1.33 mmol) and the reaction heated to reflux for 3 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with methanol and dichloromethane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**P-1717**, 9.3 mg). MS (ESI) $[M+H^+]^+ = 408.5$.

[0407] Additional compounds are prepared following the protocol of Scheme 22, where 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. Compounds are prepared optionally replacing 6-trifluoromethyl-pyridine-3-carbaldehyde **160** with a suitable aldehyde in step 3. The following compounds are made using this procedure. Compounds in the following table were characterized by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1711**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1712**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(4-ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1713**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1714**),

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1715**),

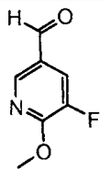
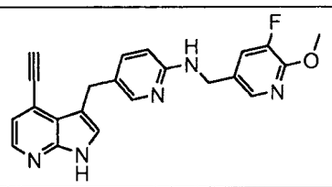
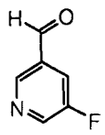
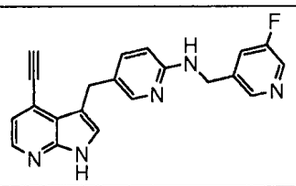
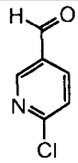
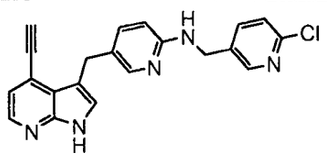
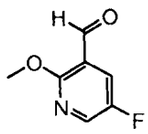
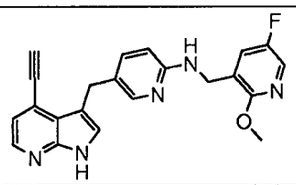
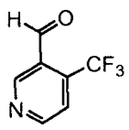
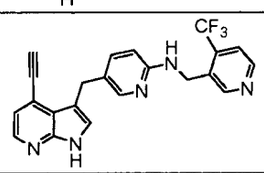
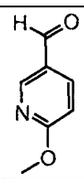
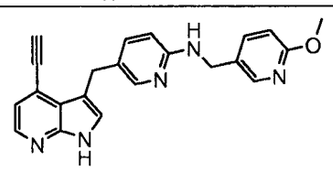
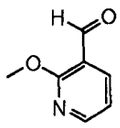
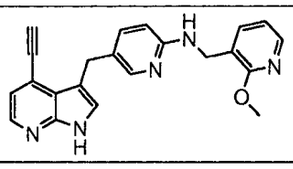
[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1716**), and

[5-(4-Ethynyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1718**).

The following table indicates the aldehyde compound (column 2) used in step 3 to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

Compound number	Aldehyde	Compound	MS (ESI) $[M+H^+]^+$

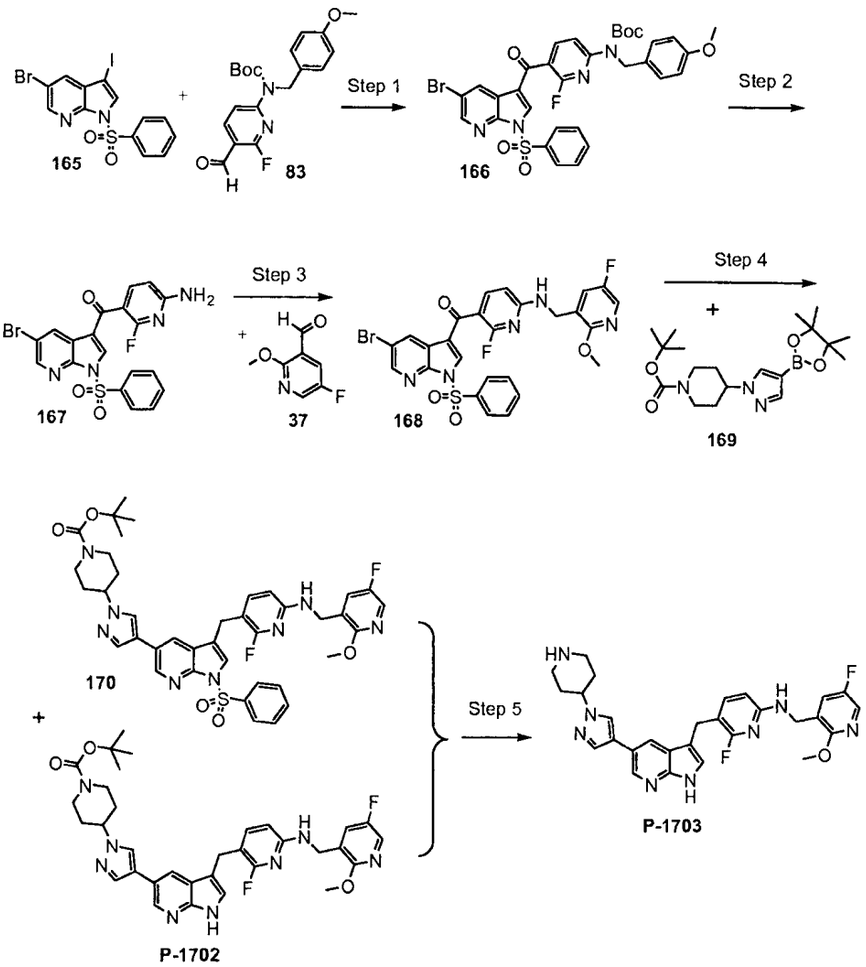
120

P-1711			
P-1712			
P-1713			
P-1714			
P-1715			
P-1716			
P-1718			

Example 23: Synthesis of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine P-1703.

[0408] (5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine **P-1703** was prepared in five steps from 1-benzenesulfonyl-5-bromo-3-iodo-1H-pyrrolo[2,3-b]pyridine **165** and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **83** as shown in Scheme 23.

Scheme 23



Step 1 – Preparation of {5-[(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (166):

[0409] To a solution of 1-benzenesulfonyl-5-bromo-3-iodo-1H-pyrrolo[2,3-b]pyridine (**165**, 1.00 g, 2.16 mmol) in 7 mL of tetrahydrofuran at -50 °C under nitrogen, isopropylmagnesium chloride (1.18 mL, 2.35 mmol) was added slowly. The reaction was warmed to 5 °C over 70 minutes, then cooled to -45 °C and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**83**, 0.678 g, 1.88 mmol) in 3.0 mL of tetrahydrofuran was added. The reaction was allowed to warm to room temperature over 2-3 hours. The reaction was mixed with aqueous 1 N citric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as a white solid (**166**, 1.155 g). MS (ESI) $[M+H^+]^+$ = 696.4 and 698.3.

*Step 2 – Preparation of 5-(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine (**167**):*

[0410] In a round bottom flask, {5-[(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**166**, 1.15 g, 1.65 mmol) was combined with 50 mL of 1,2-dichloroethane, trifluoroacetic acid (0.635 mL, 8.24 mmol), and triethylsilane (1.32 mL, 8.24 mmol). The reaction was heated at reflux for 20 hours, then concentrated under vacuum. The residue was dissolved in 10 mL of trifluoroacetic acid and stirred at room temperature for 18 hours, then concentrated under vacuum and combined with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate, water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound (**167**, 403 mg). MS (ESI) $[M-H^+]^-$ = 460.8 and 462.8.

*Step 3 – Preparation of [5-(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**168**):*

[0411] To 5-(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine (**167**, 0.342 g, 0.741 mmol) in 10 mL of acetonitrile, 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (**37**, 0.118 g, 0.763 mmol), triethylsilane (0.529 mL, 3.71 mmol) and trifluoroacetic acid (0.286 mL, 3.71 mmol) were added. The reaction was heated at 80 °C for 4 hours, then concentrated under vacuum and combined with aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compound as an off-white solid (**168**, 367 mg). MS (ESI) $[M-H^+]^-$ = 599.6 and 601.6.

*Step 4 – Preparation of 4-[4-(1-benzenesulfonyl-3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**170**) and 4-[4-(3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**P-1702**):*

[0412] In a microwave vial, [5-(1-benzenesulfonyl-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**168**, 218 mg, 0.363 mmol) and 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**169**, 205 mg, 0.545 mmol) were combined and 2.22 mL of acetonitrile and potassium carbonate (1.11 mL, 1.0 M in water, 1.11 mmol) were added. Then [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27 mg, 0.037 mmol) was added to the reaction mixture and heated at 160 °C in a microwave for 5 minutes. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with ethyl acetate and hexane. Appropriate fractions were combined and concentrated under vacuum to provide the desired compounds (**170**, 137 mg) and (**P-1702**, 66 mg). **170** MS (ESI) $[M+H^+]^+$ = 770.7. **P-1702** MS (ESI) $[M+H^+]^+$ = 631.1.

*Step 5 -- Preparation of (5-fluoro-2-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1703**):*

[0413] In a vial, 4-[4-(1-benzenesulfonyl-3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**170**, 0.137 g, 0.178 mmol) was dissolved in a solution of potassium hydroxide (0.392 g, 6.99 mmol) in 7.0 mL of methanol and the reaction was heated at 50 °C for 3 hours. Aqueous 1 M citric acid was added, then the reaction was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. 4-[4-(3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester (**P-1702**, 56 mg, 0.0888 mmol) was combined with this and 10 mL of dichloromethane and trifluoroacetic acid (0.50 mL, 6.5 mmol) were added, then stirred at room temperature for 2 hours. Aqueous saturated sodium bicarbonate was added to pH~8, then concentrated under vacuum and ethyl acetate and water were added. The organic layer was isolated and washed with aqueous saturated sodium bicarbonate, then dried with magnesium sulfate, filtered and the filtrate concentrated under vacuum to provide the desired compound as a yellow solid (**P-1703**, 74 mg). MS (ESI) $[M+H^+]^+$ = 631.1.

[0414] Additional compounds are prepared following the protocol of Scheme 23, where 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. Compounds are prepared optionally replacing 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37**, with a suitable aldehyde in step 3. The following compounds are made using this procedure. Compounds in the following table were characterized by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1704**),

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{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1705**),

(6-Chloro-pyridin-3-ylmethyl)-{6-fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (**P-1706**),

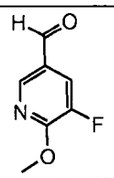
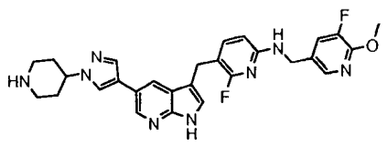
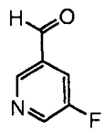
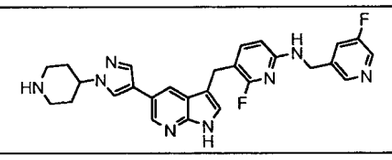
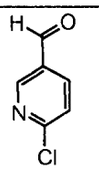
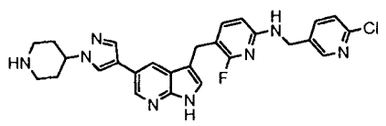
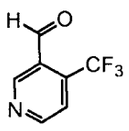
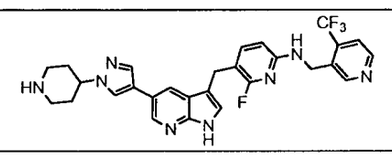
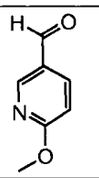
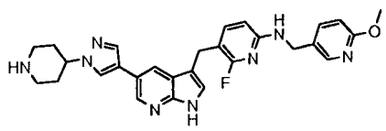
{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1707**),

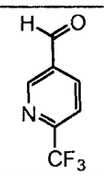
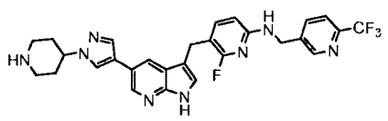
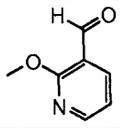
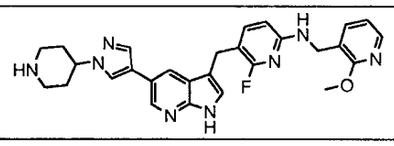
{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1708**),

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1709**), and

{6-Fluoro-5-[5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1710**).

The following table indicates the aldehyde compound (column 2) used in step 3 to afford the desired compound (column 3). The compound number is provided in column 1, and the observed mass is in column 4.

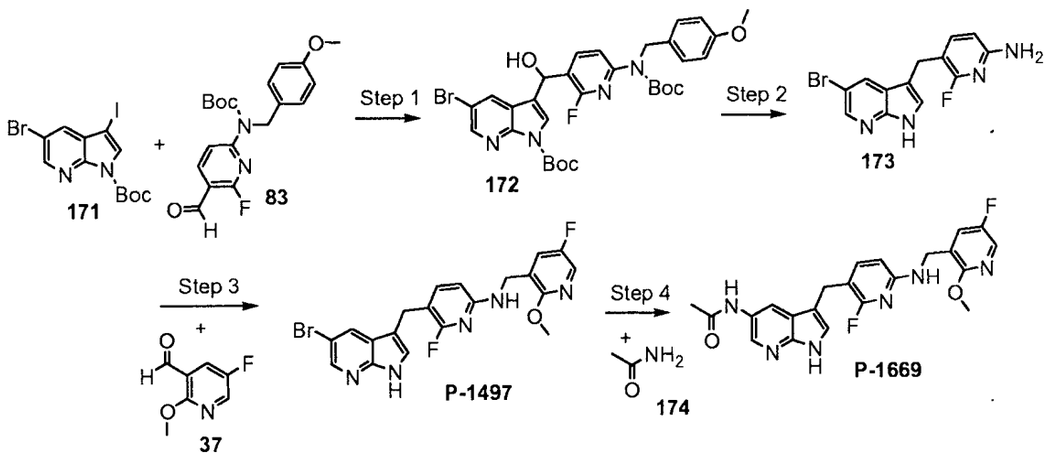
Compound number	Aldehyde	Compound	MS (ESI) $[M+H^+]^+$
P-1704			
P-1705			
P-1706			
P-1707			
P-1708			

P-1709			
P-1710			

Example 24: Synthesis of N-(3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide P-1669.

[0415] N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide **P-1669** is prepared in four steps from 5-bromo-3-iodo-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester **171** and (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester **83** as shown in Scheme 24.

Scheme 24



Step 1 – Preparation of 5-bromo-3-({6-[tert-butoxycarbonyl-(4-methoxy-benzyl)-amino]-2-fluoro-pyridin-3-yl}-hydroxy-methyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (172):

[0416] To 5-bromo-3-iodo-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**171**, 1 equivalent) in 500 mL of tetrahydrofuran under nitrogen at -20 °C, iso-propylmagnesium chloride (1.2 equivalent) is added. The reaction is allowed to warm to 0 °C over 30 minutes, then cooled to -40 °C, followed by adding (6-fluoro-5-formyl-pyridin-2-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester (**83**, 0.8 equivalent). 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 concentrated under vacuum to provide the desired compound, used in the next step without further purification.

Step 2 – Preparation of 5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine (173):

[0417] To 5-bromo-3-({6-[tert-butoxycarbonyl-(4-methoxy-benzyl)-amino]-2-fluoro-pyridin-3-yl}-hydroxy-methyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**172**, 1 equivalent) in 451 mL of acetonitrile, triethylsilane (10 equivalents) and trifluoroacetic acid (10 equivalents) are added. The reaction is stirred at 80 °C for several hours, then concentrated under vacuum. The resulting material is taken up in 250 mL of dichloromethane and 250 mL of trifluoroacetic acid is added, then stirred at reflux for several hours. The reaction is concentrated under vacuum and the resulting material is taken up in ethyl acetate and extraction with the addition of aqueous saturated potassium carbonate. The organic layer is concentrated under vacuum and the resulting material is purified by silica gel column chromatography, eluting with 0-5% methanol in dichloromethane. Appropriate fractions are combined and concentrated under vacuum to provide the desired compound.

*Step 3 – Preparation of [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1497**):*

[0418] To 5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-ylamine (**173**, 1 equivalent) and 5-fluoro-2-methoxy-pyridine-3-carbaldehyde (**37**, 1 equivalent), triethylsilane (4 equivalents) and trifluoroacetic acid (4 equivalents) are added. The reaction is stirred at 80 °C for several hours, then concentrated under vacuum. The resulting material is taken up in ethyl acetate and extracted with addition of aqueous potassium carbonate. The organic layer is concentrated under vacuum, then triturated with dichloromethane to provide the desired compound.

*Step 4 – Preparation of N-(3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1669**):*

[0419] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1497**, 1 equivalent) is dissolved in 25 mL of dioxane in a sealable vial. Cesium carbonate (2.1 equivalents), copper(I) iodide (1.5 equivalents), acetamide (**174**, 22 equivalents) and N,N'-dimethylethylenediamine (17 equivalents) are added. The vial is sealed and heated at 100 °C overnight. The reaction is added to ethyl acetate and brine and extracted. The organic layer is concentrated under vacuum and the resulting material dissolved in dichloromethane and purified by silica gel column chromatography, eluting with 0-10% methanol in dichloromethane. Appropriate fractions are concentrated, and the material dissolved in tetrahydrofuran for further purification on a C18 reverse phase column, eluting with 0-100% methanol (with 10% tetrahydrofuran)/water. Appropriated fractions are combined and concentrated under vacuum. The resulting material is triturated with methyl tert-butyl ether and filtered, washing with methyl tert-butyl ether, then heptane. The solid is dried under vacuum to provide the desired compound.

[0420] Additional compounds are prepared following the protocol of Scheme 24, where 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. Compounds are prepared optionally replacing 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37**, with a suitable aldehyde in step 3 and optionally replacing acetamide **174** with methanesulfonamide in step 4. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

N-(3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1670**),

N-(3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1671**),

N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1672**),

N-(3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1673**),

N-(3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1674**),

N-(3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1675**),

N-(3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1676**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1677**),

N-(3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1678**),

N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1679**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1680**),

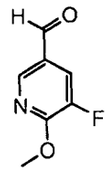
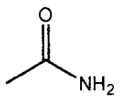
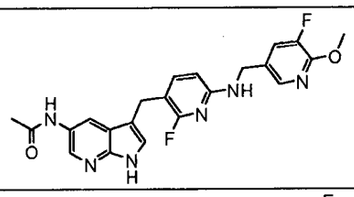
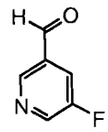
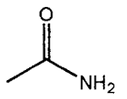
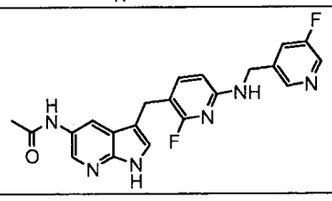
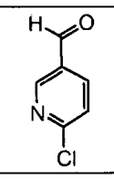
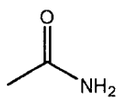
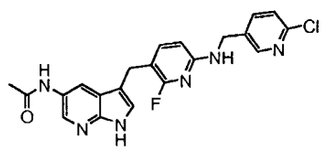
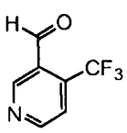
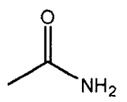
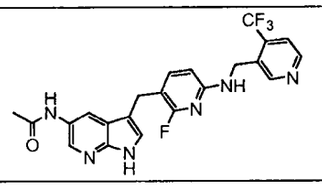
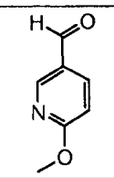
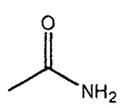
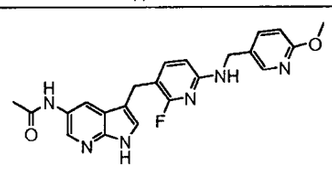
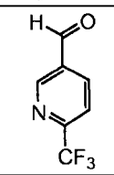
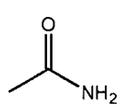
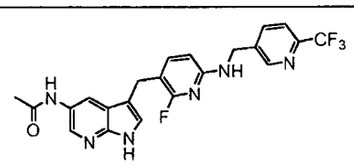
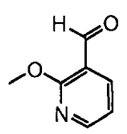
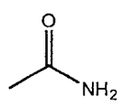
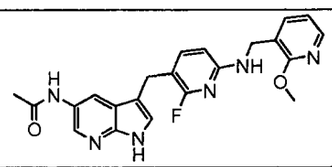
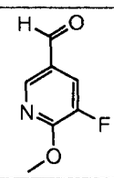
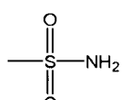
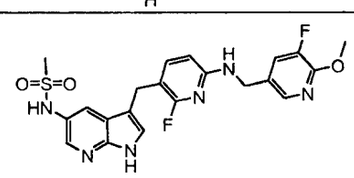
N-(3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1681**),

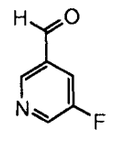
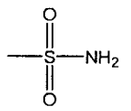
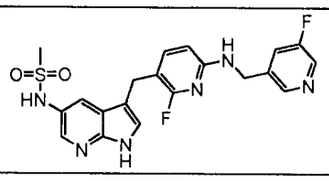
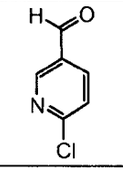
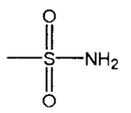
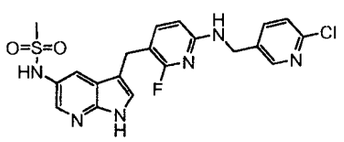
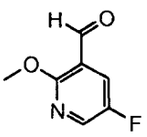
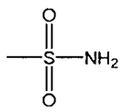
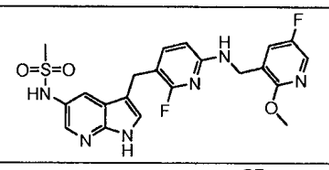
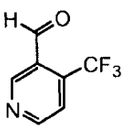
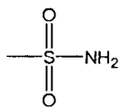
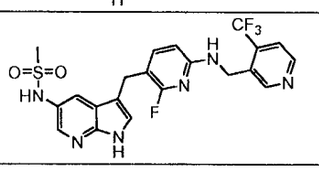
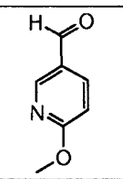
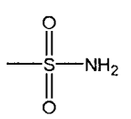
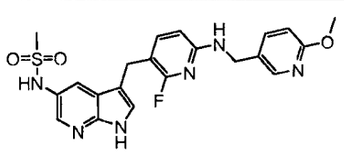
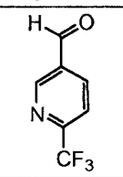
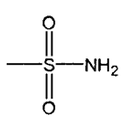
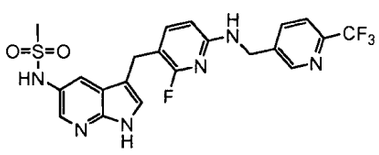
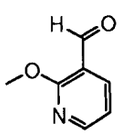
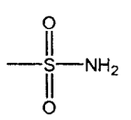
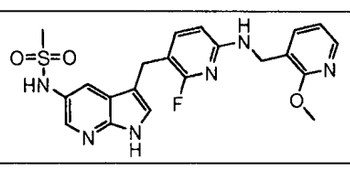
N-(3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1682**),

N-(3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1683**), and

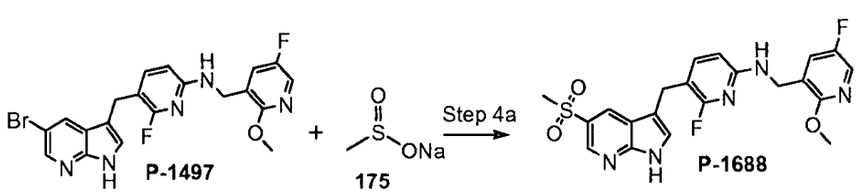
N-(3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1684**).

The following table indicates the aldehyde compound (column 2) used in step 3 and acetamide or methanesulfonamide (column 3) used in step 4 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

Compound number	Aldehyde	Step 4	Compound	MS (ESI) $[M+H^+]^+$
P-1670				
P-1671				
P-1672				
P-1673				
P-1674				
P-1675				
P-1676				
P-1677				

P-1678				
P-1679				
P-1680				
P-1681				
P-1682				
P-1683				
P-1684				

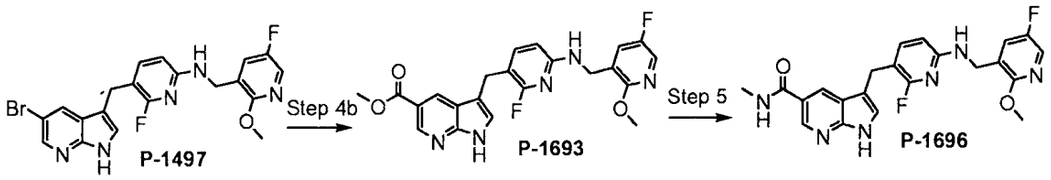
[0421] [6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine **P-1688** is prepared from [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine **P-1497** by the following step 4a.



*Step 4a – Preparation of [6-fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine **(P-1688)**:*

[0422] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1497**, 1 equivalent) is dissolved in 5 mL of dimethyl sulfoxide in a sealable vial. Copper(I) iodide (0.2 equivalent), L-proline (0.2 equivalent), sodium methanesulfinate (**175**, 1.2 equivalents), and sodium hydroxide (0.2 equivalent) are added. The vial is sealed and heated at 100 °C overnight, then additional copper(I) iodide (0.2 equivalent), L-proline (0.2 equivalent), sodium methansulfinate (1.2 equivalent), and sodium hydroxide (0.2 equivalent) are added, and the reaction is sealed and heated at 120 °C overnight. The reaction is added to ethyl acetate and brine and extracted. The organic layer is concentrated under vacuum and the resulting material dissolved in tetrahydrofuran for purification on a C18 reverse phase column, eluting with 0-100% methanol (with 10% tetrahydrofuran)/water. Appropriate fractions are combined and concentrated under vacuum. The resulting material is triturated with methyl tert-butyl ether and filtered, washing with methyl tert-butyl ether, then heptane. The solid is dried under vacuum to provide the desired compound.

[0423] 3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide **P-1696** is prepared from [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine **P-1497** by the following steps 4b and 5.



*Step 4b – Preparation of 3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester **(P-1693)**:*

[0424] In a 2L Parr bomb, [5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1497**, 1 equivalent), triethylamine (2 equivalents), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.03 equivalents) are combined with 300 ml of methanol. The reaction is heated at 100 °C under 100 psi of carbon monoxide overnight. The reaction mixture is concentrated under vacuum, taken up in ethyl acetate and washed with water. The organic layer is concentrated under vacuum, the residue dissolved in dichloromethane and purified by silica gel column chromatography, eluting with 0-10% methanol in dichloromethane. Appropriated fractions are combined and concentrated under vacuum to provide the desired compound.

*Step 5 – Preparation of 3-{2-fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1696**):*

[0425] 3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**P-1693**, 1 equivalent) is slurried with methylamine (2N in methanol, 15 equivalents) in a scalable vial, sealed and heated at 50 °C overnight. Additional methylamine (2N in methanol, 15 equivalents) is added and heated at 50 °C overnight. The reaction is concentrated under vacuum, the residue dissolved in tetrahydrofuran for purification on a C18 reverse phase column, eluting with 0-100% methanol (with 10% tetrahydrofuran)/water. Appropriated fractions are combined and concentrated under vacuum. The resulting material is triturated with ethyl acetate/heptane and filtered, washing with heptane. The solid is dried under vacuum to provide the desired compound.

[0426] Additional compounds are prepared following the protocol of Scheme 24, using steps 4a or steps 4b and step 5, where 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. Compounds are prepared optionally replacing 5-fluoro-2-methoxy-pyridine-3-carbaldehyde **37**, with a suitable aldehyde in step 3. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1685**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1686**),

(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1687**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1689**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1690**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1691**),

[6-Fluoro-5-(5-methanesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1692**),

3-{2-Fluoro-6-[(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1694**),

3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-

5-carboxylic acid methylamide (**P-1695**),

3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1697**),

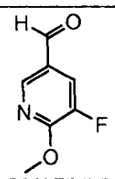
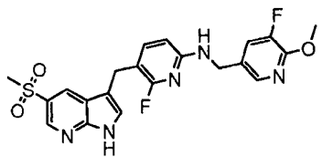
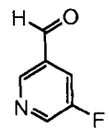
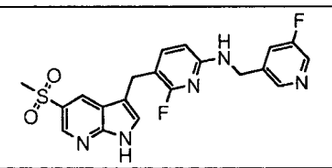
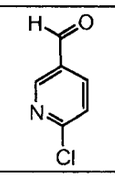
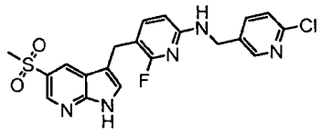
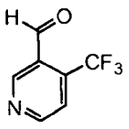
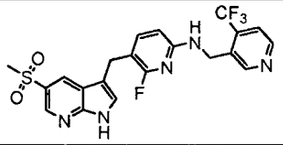
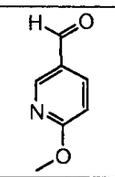
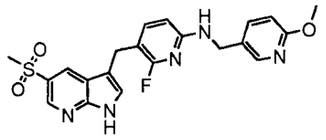
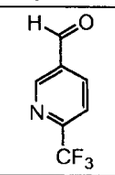
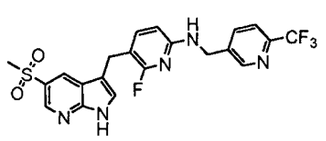
3-{2-Fluoro-6-[(4-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1698**),

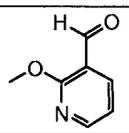
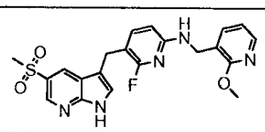
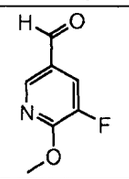
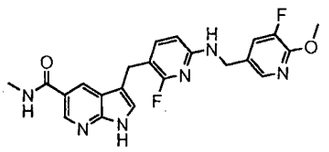
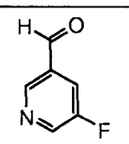
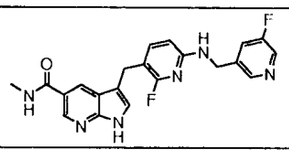
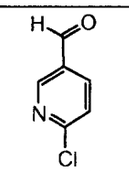
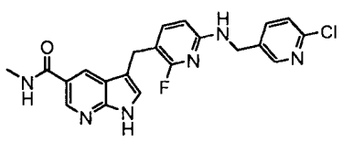
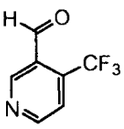
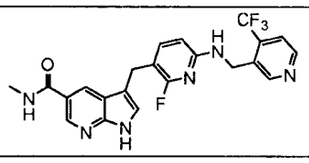
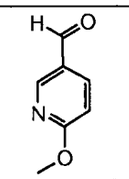
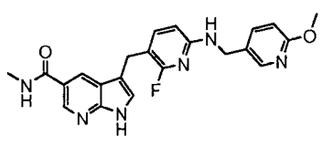
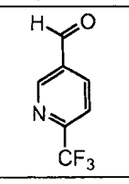
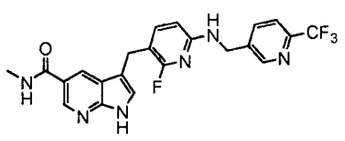
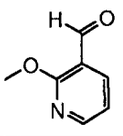
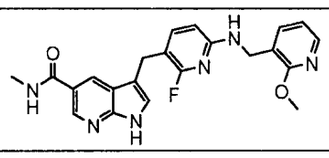
3-{2-Fluoro-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1699**),

3-{2-Fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1700**), and

3-{2-Fluoro-6-[(2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methylamide (**P-1701**).

The following table indicates the aldehyde compound (column 2) used in step 3 and whether step 4a or step 4b/5 is used (column 3) used in step 4 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

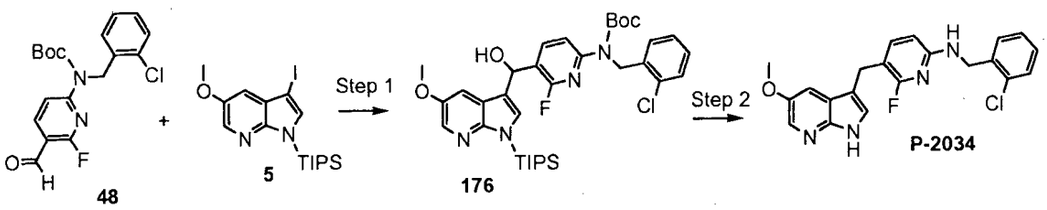
Compound number	Aldehyde	Steps used	Compound	MS (ESI) $[M+H^+]^+$
P-1685		4a		
P-1686		4a		
P-1687		4a		
P-1689		4a		
P-1690		4a		
P-1691		4a		

P-1692		4a		
P-1694		4b/5		
P-1695		4b/5		
P-1697		4b/5		
P-1698		4b/5		
P-1699		4b/5		
P-1700		4b/5		
P-1701		4b/5		

Example 25: Synthesis of (2-chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-2034.

[0427] (2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-2034** was prepared in two steps from (2-chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **48** and 3-iodo-5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **5** as shown in Scheme 25.

Scheme 25



Step 1 – Preparation of (2-chloro-benzyl)-{6-fluoro-5-[hydroxy-(5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (176):

[0428] To 3-iodo-5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**5**, 0.49 g, 1.14 mmol) in 6.8 mL of tetrahydrofuran at -50 °C under nitrogen, isopropylmagnesium chloride (0.569 mL, 2.0 M in tetrahydrofuran, 1.14 mmol) was added slowly. The reaction was allowed to warm to 5 °C over 70 minutes, then cooled to -60 °C and (2-chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**48**, 0.23 g, 0.63 mmol) in 30.0 mL of tetrahydrofuran was added. The reaction was allowed to warm to room temperature over 1 hour, then poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and the sólvents removed under vacuum to provide the desired compound as a white solid (**176**, 0.400 g). MS (ESI) $[M+H^+]^+ = 669.4$.

*Step 2 – Preparation of (2-chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2034**):*

[0429] To (2-chloro-benzyl)-{6-fluoro-5-[hydroxy-(5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2;3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-carbamic acid tert-butyl ester (**176**, 400 mg, 0.598 mmol) in 20.0 mL of dichloromethane, triethylsilane (2.00 mL, 12.5 mmol) and trifluoroacetic acid (1.00 mL, 13.0 mmol) were added. The reaction was stirred at room temperature for 4 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The resulting material was purified by silica gel column chromatography eluting with 20-100% ethyl acetate in hexane. Appropriate fractions were combined and the solvents removed under vacuum to provide the desired compound as a white solid (**P-2034**, 60.7 mg). MS (ESI) $[M+H^+]^+ = 397.1$.

[0430] Additional compounds are prepared following the protocol of Scheme 25, where 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. Compounds are prepared using a suitable 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine in place of 3-iodo-5-methoxy-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **5** and

suitable aldehyde in place (2-chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **48** in step 1. The following compounds are made using this procedure. Compounds in the following table were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1499**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1500**),

[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1501**),

(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1513**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1514**),

(6-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1515**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1516**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1517**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1518**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1519**),

(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1520**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-1521**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1522**),

(6-Chloro-pyridin-3-ylmethyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1523**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-1524**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1525**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1526**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1527**),
(6-Methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1532**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1533**),
(5-Fluoro-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1534**),
(6-Chloro-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1535**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1536**),
[6-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1537**),
[6-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1538**),
(2-Methoxy-pyridin-3-ylmethyl)-[6-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1539**),
(6-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1554**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1555**),
(5-Fluoro-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1556**),
(6-Chloro-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1557**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1558**),
[3-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1559**),
[3-Methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1560**),
(2-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1561**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1562**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-

ylmethyl)-pyridin-2-yl]-amine (**P-1563**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1564**),
(6-Chloro-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1565**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[3-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1566**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1567**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1568**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1579**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1580**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-1581**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1582**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1597**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1598**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-1607**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1608**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1609**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1630**),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1631**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1632**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-1633**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1634**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1635**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1636**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1637**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-1727**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-1728**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-1729**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1730**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1731**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1732**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-amine (**P-1733**),
[6-Fluoro-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-1734**),
(2-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2035**),
(2-Chloro-benzyl)-[5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2036**),
(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2040**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2042**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-

ylmethyl)-amine (**P-2043**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2044**),
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2045**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2047**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2050**),
(2-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2051**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2052**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2057**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-2058**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2062**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2063**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2064**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-4-ylmethyl)-amine (**P-2065**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2067**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2070**),
(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2071**),

(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2072**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2073**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2075**),
(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2135**),
(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2136**),
[3-Methoxy-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2143**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2144**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2145**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2146**),
[3-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2147**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2152**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2153**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2154**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2155**),
3-{[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-methyl}-5-fluoro-1-methyl-1H-pyridin-2-one (**P-2157**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2158**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2159**),
(6-Methoxy-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-2162**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-

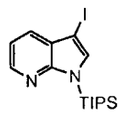
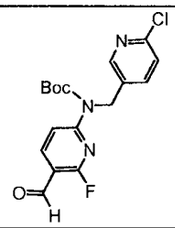
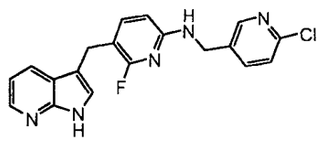
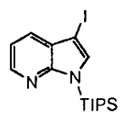
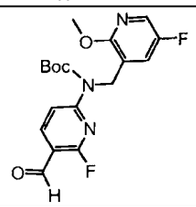
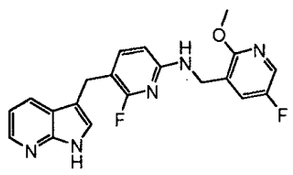
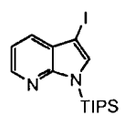
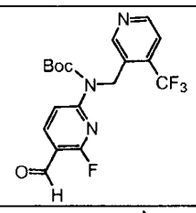
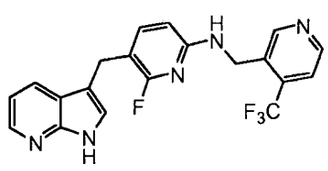
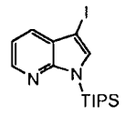
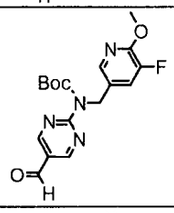
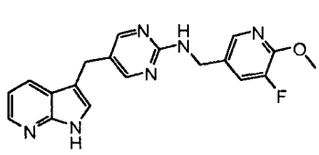
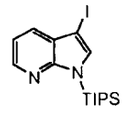
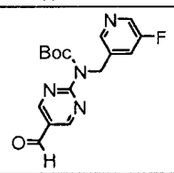
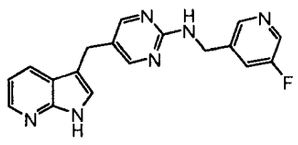
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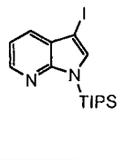
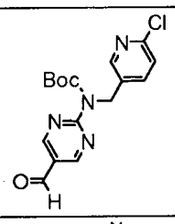
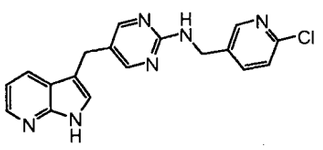
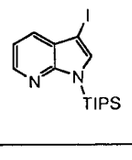
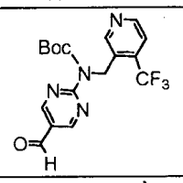
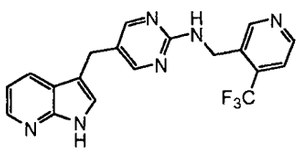
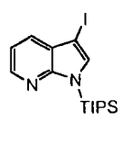
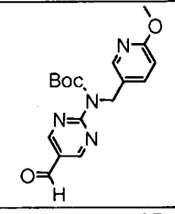
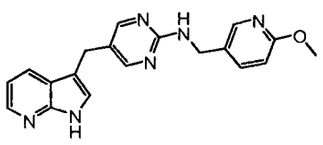
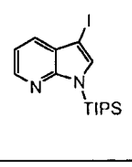
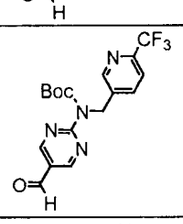
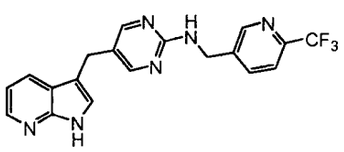
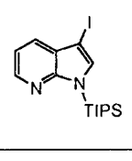
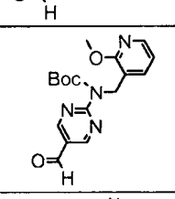
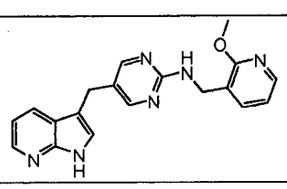
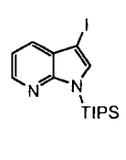
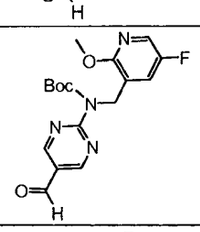
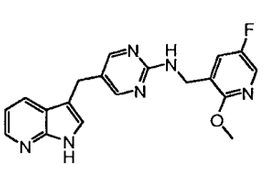
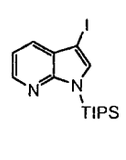
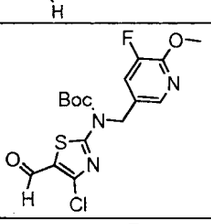
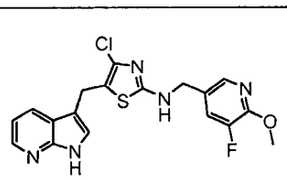
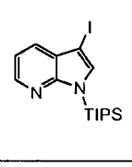
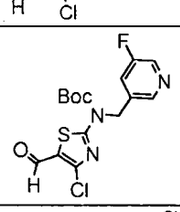
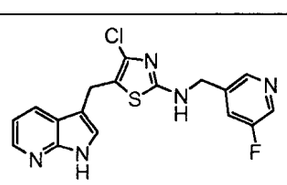
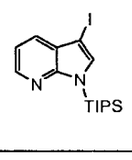
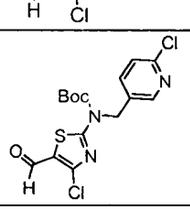
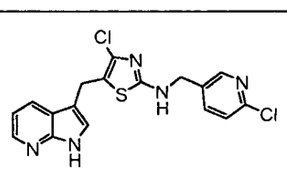
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**P-2164**),

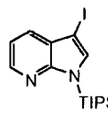
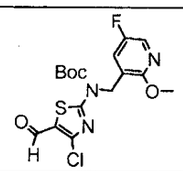
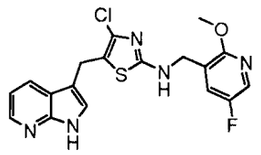
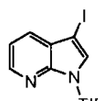
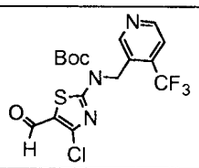
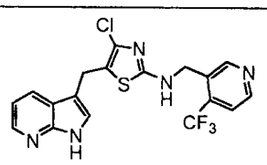
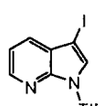
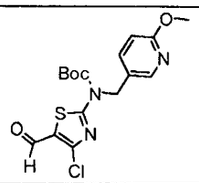
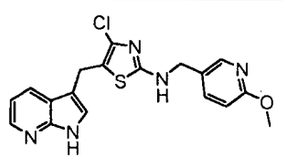
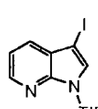
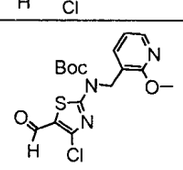
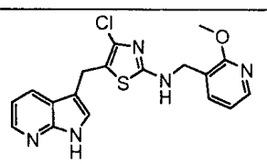
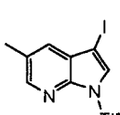
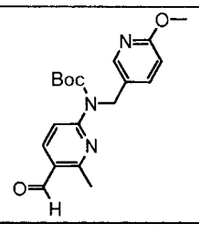
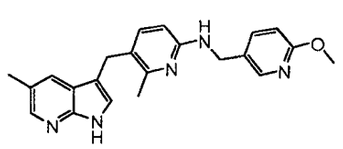
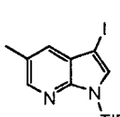
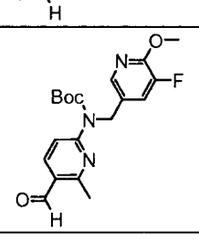
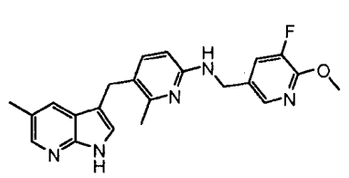
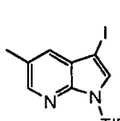
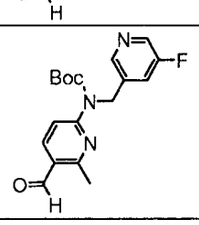
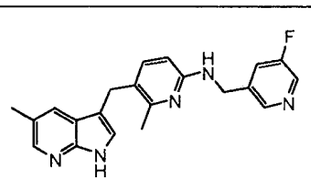
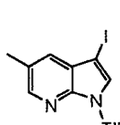
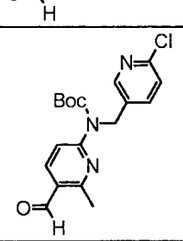
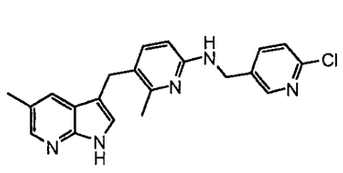
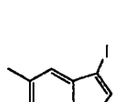
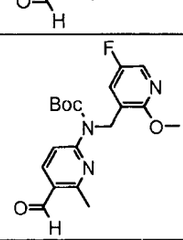
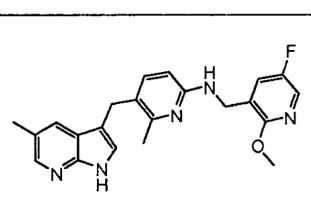
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**), and

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2172**).

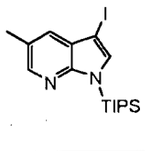
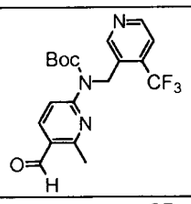
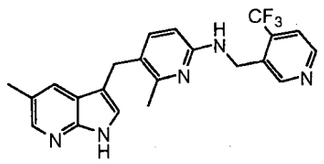
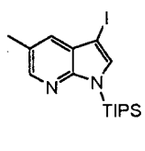
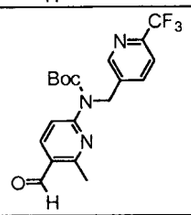
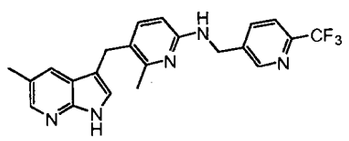
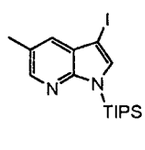
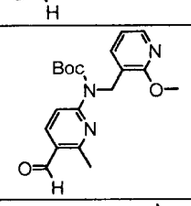
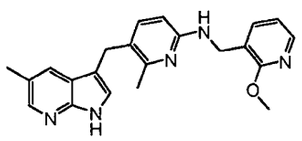
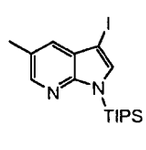
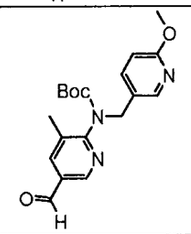
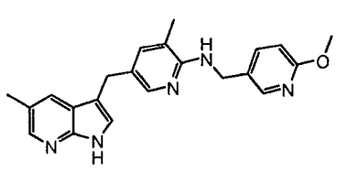
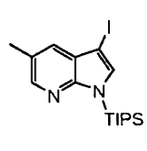
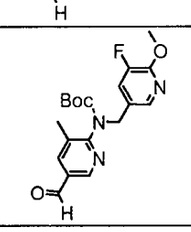
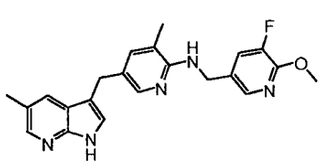
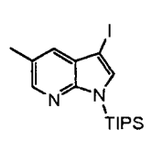
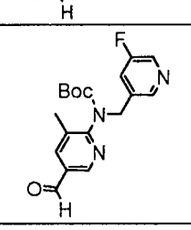
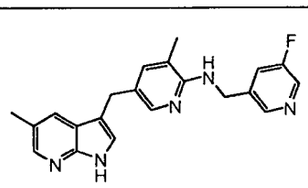
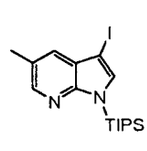
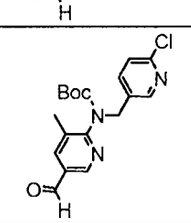
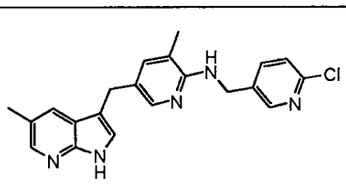
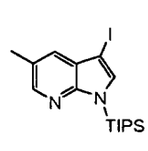
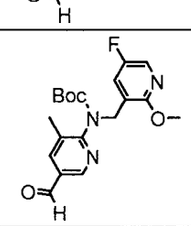
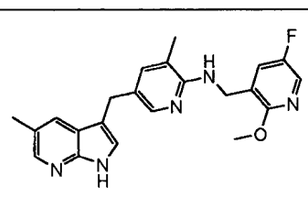
The following table indicates the 1H-pyrrolo[2,3-b]pyridine compound (column 2) and aldehyde compound (column 3) used in step 1 to afford the desired compound (column 4). The compound number is provided in column 1, and the observed mass is in column 5.

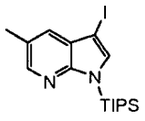
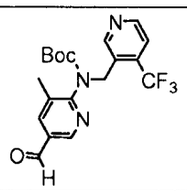
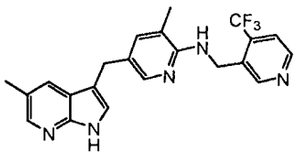
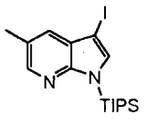
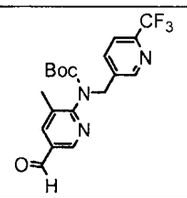
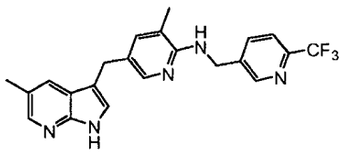
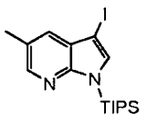
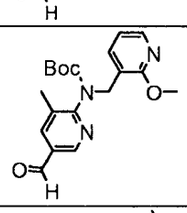
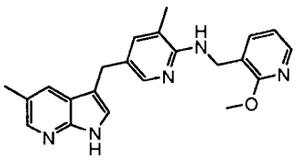
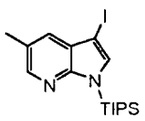
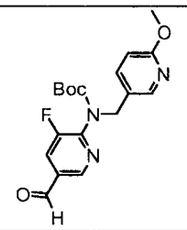
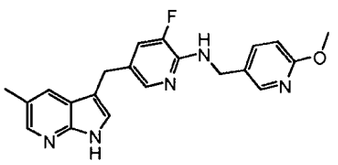
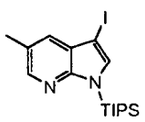
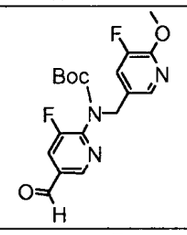
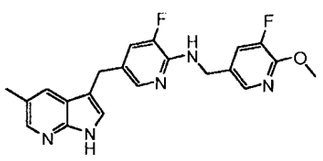
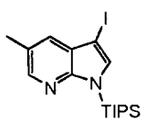
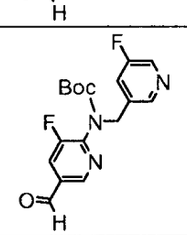
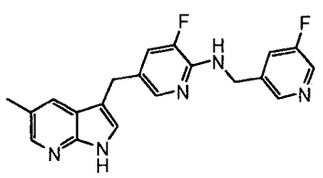
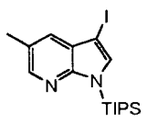
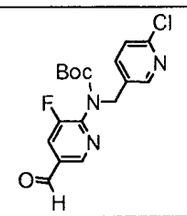
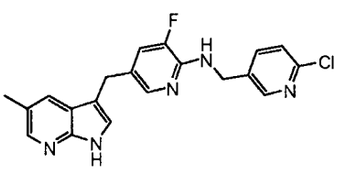
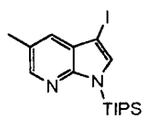
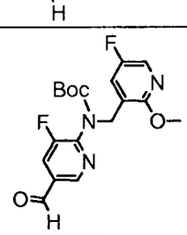
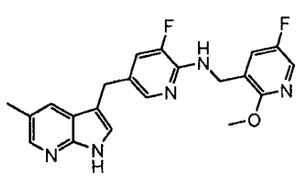
Comp. number	1H-pyrrolo[2,3-b]pyridine	Aldehyde	Compound structure	MS (ESI) $[M+H^+]^+$
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P-1500				
P-1501				
P-1513				
P-1514				

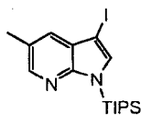
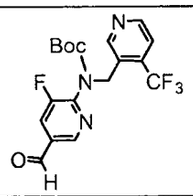
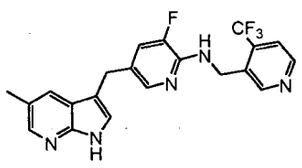
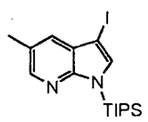
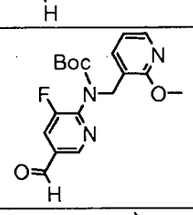
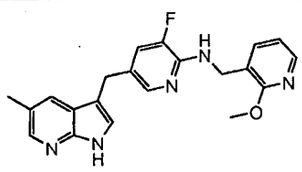
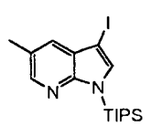
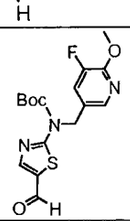
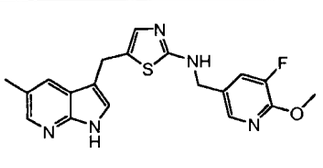
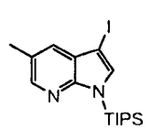
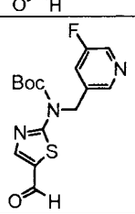
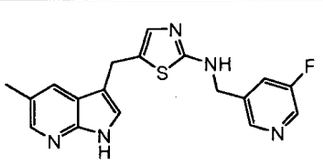
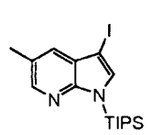
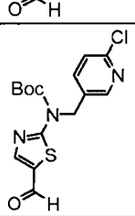
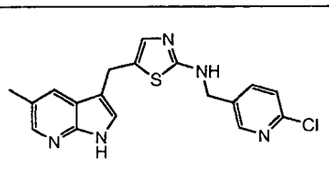
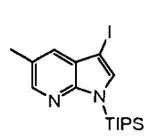
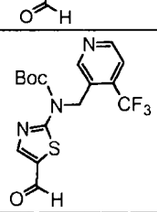
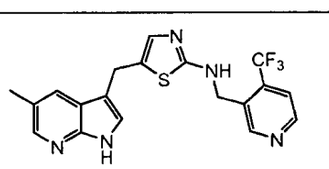
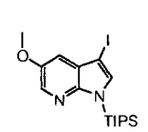
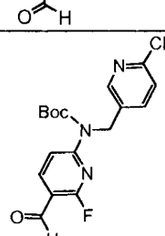
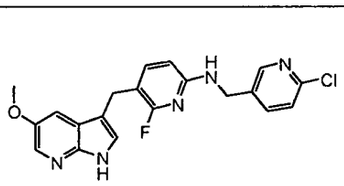
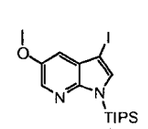
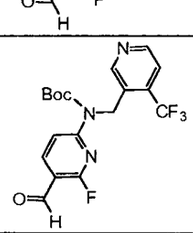
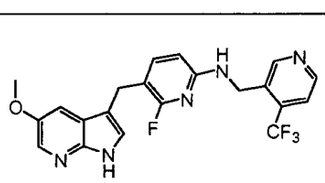
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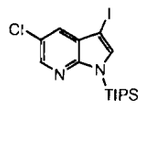
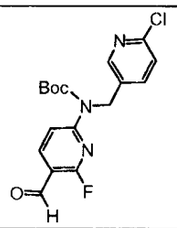
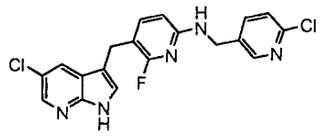
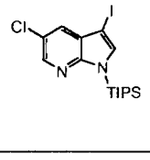
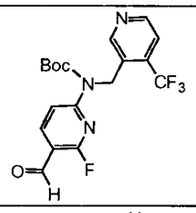
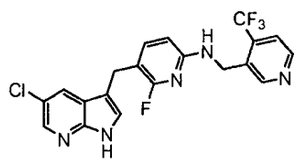
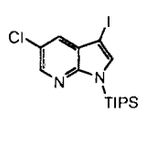
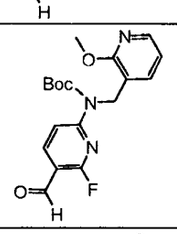
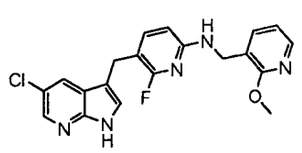
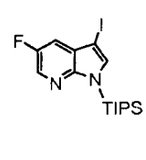
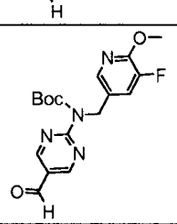
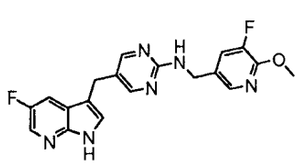
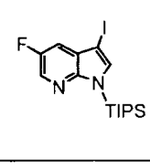
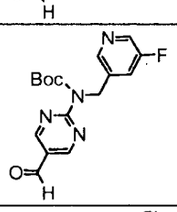
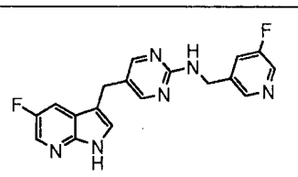
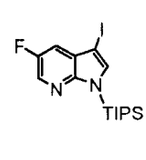
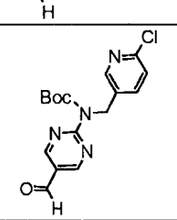
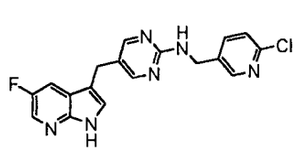
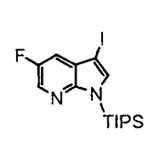
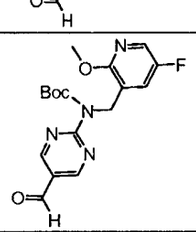
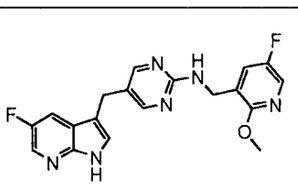
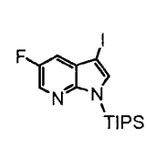
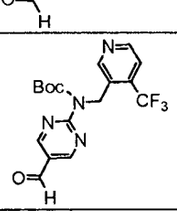
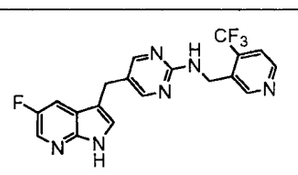
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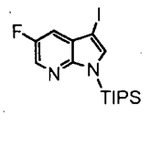
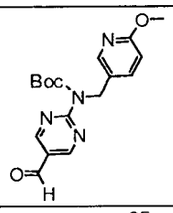
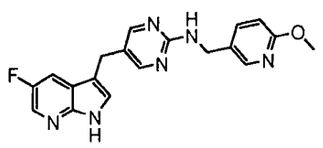
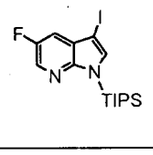
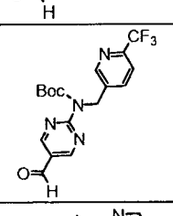
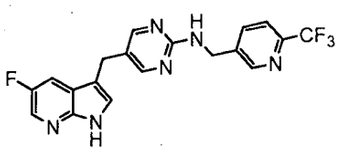
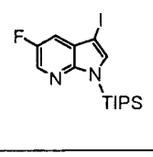
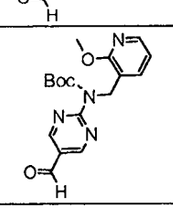
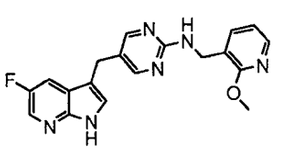
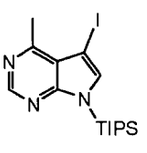
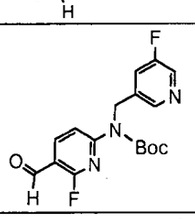
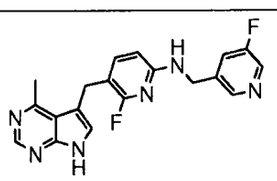
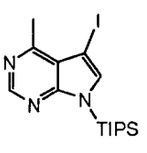
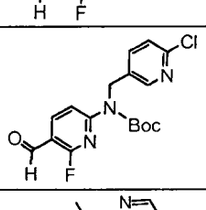
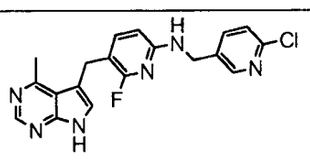
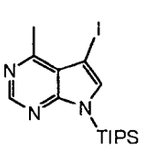
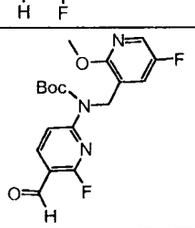
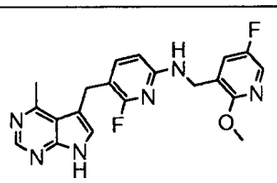
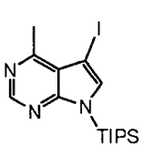
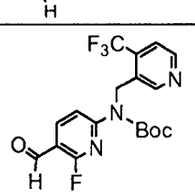
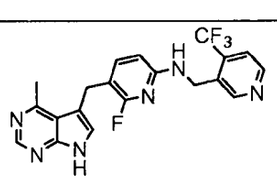
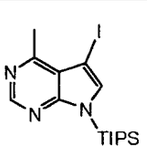
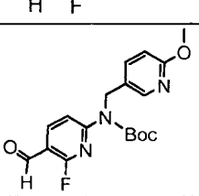
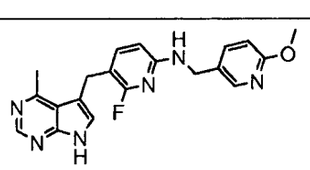
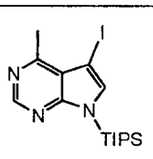
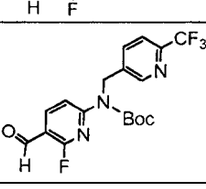
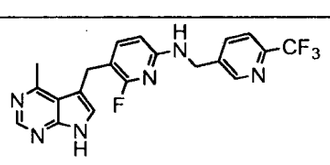
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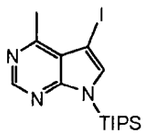
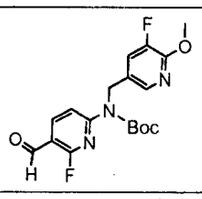
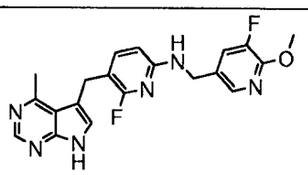
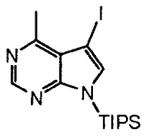
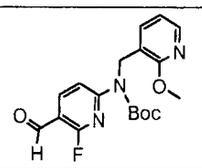
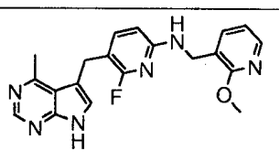
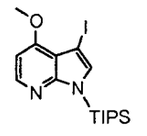
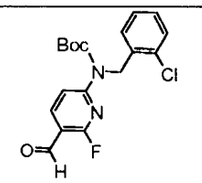
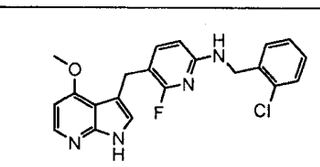
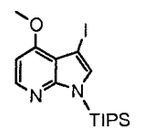
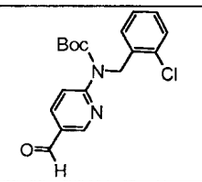
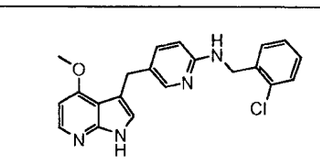
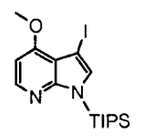
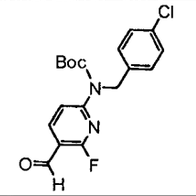
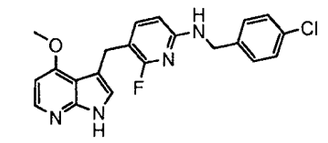
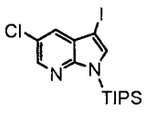
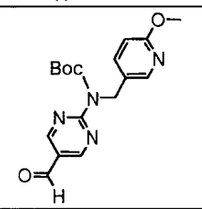
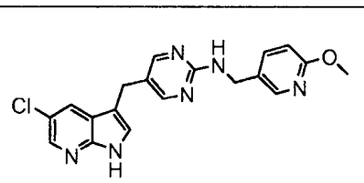
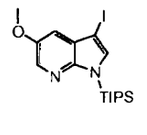
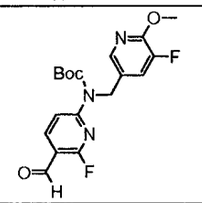
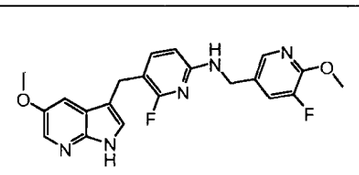
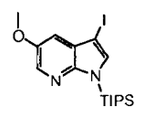
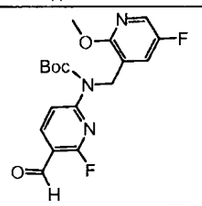
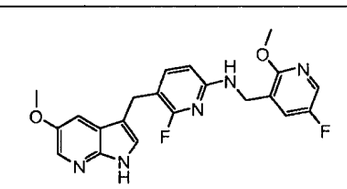
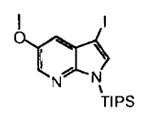
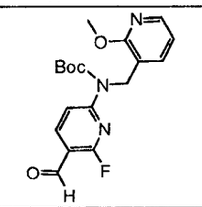
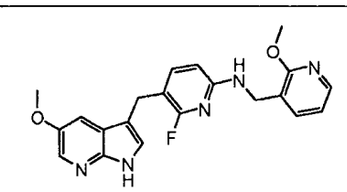
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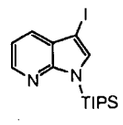
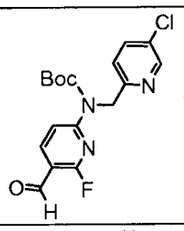
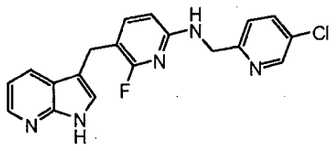
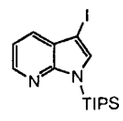
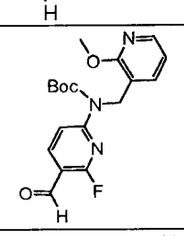
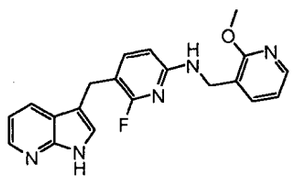
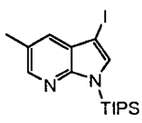
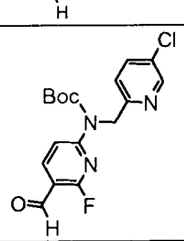
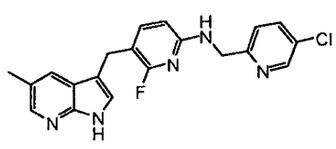
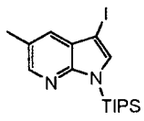
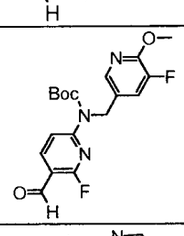
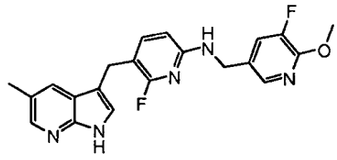
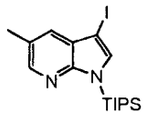
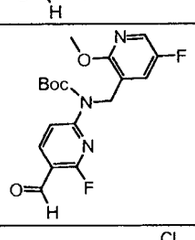
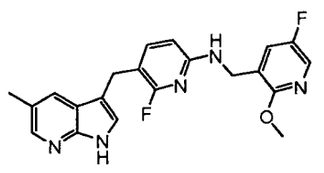
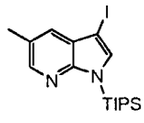
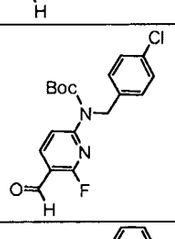
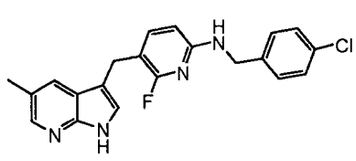
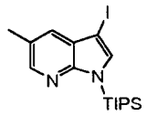
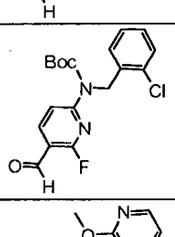
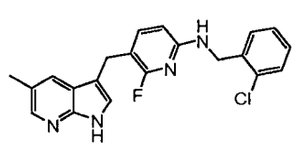
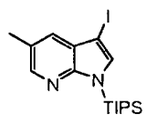
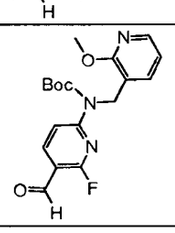
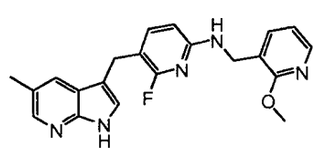
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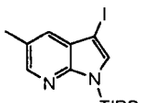
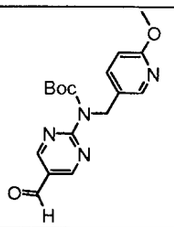
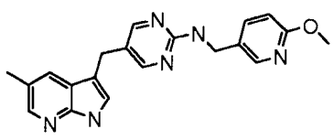
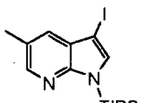
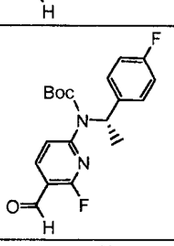
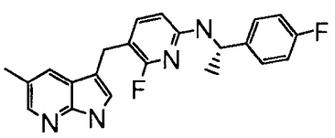
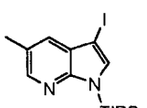
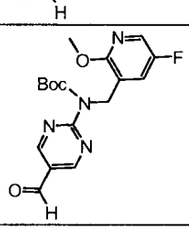
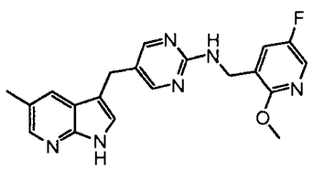
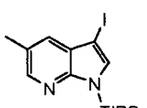
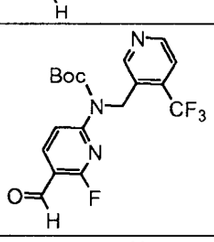
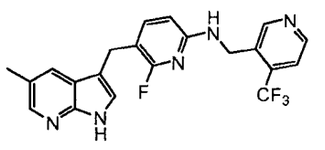
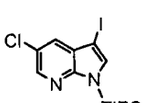
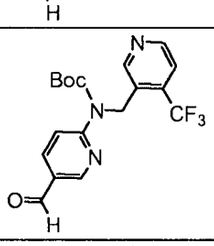
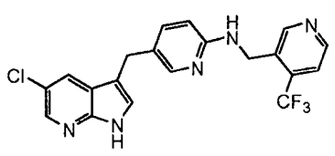
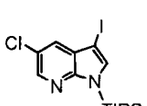
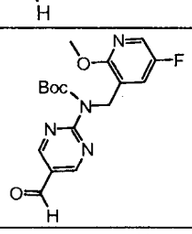
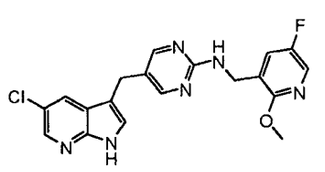
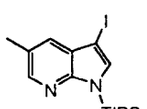
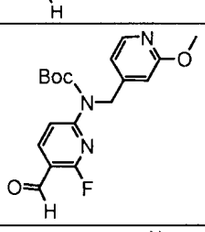
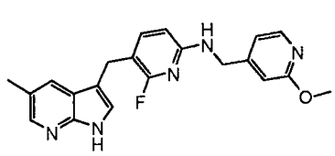
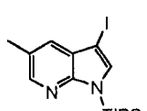
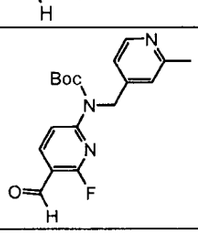
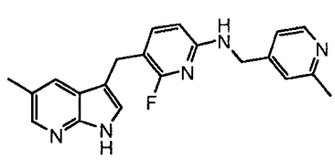
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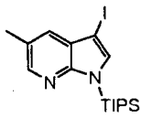
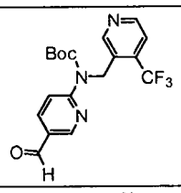
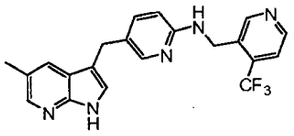
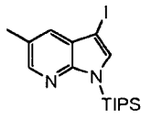
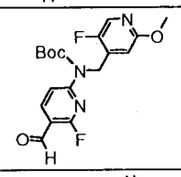
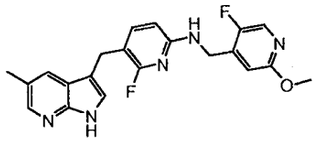
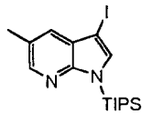
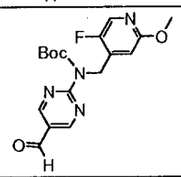
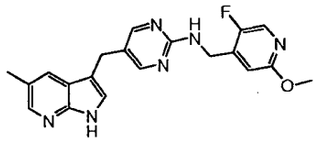
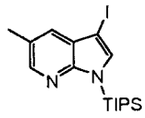
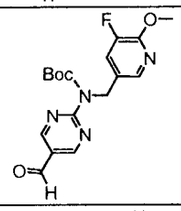
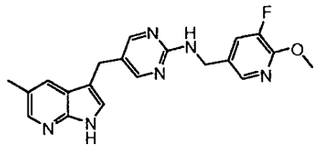
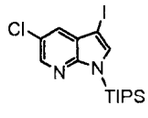
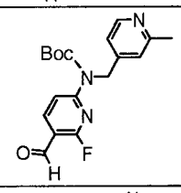
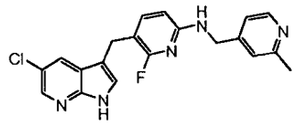
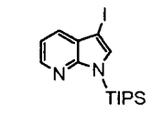
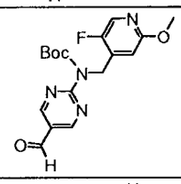
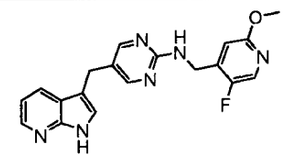
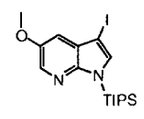
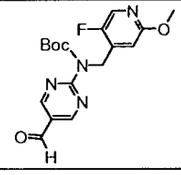
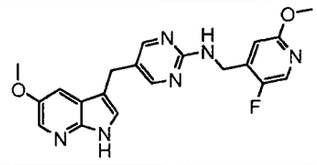
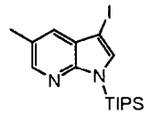
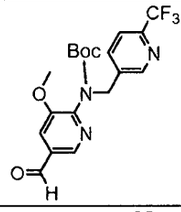
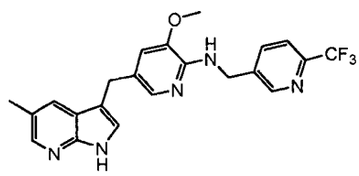
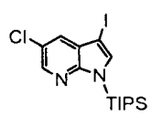
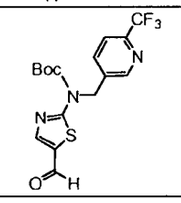
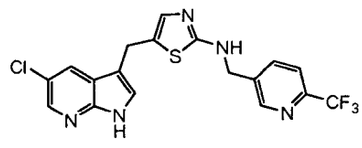
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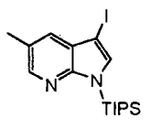
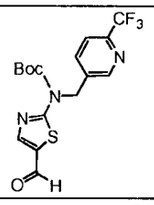
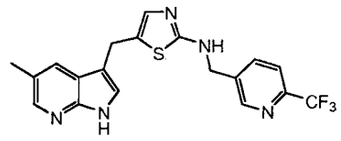
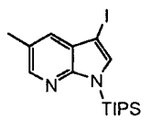
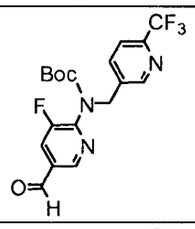
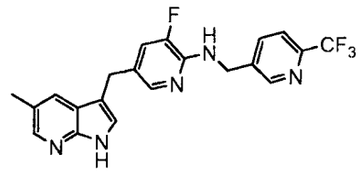
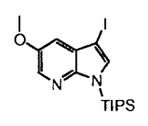
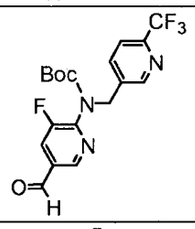
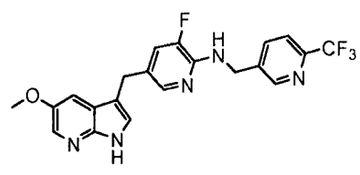
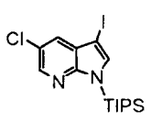
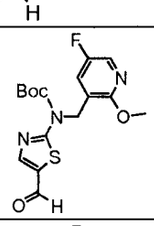
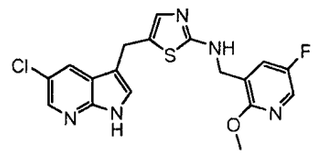
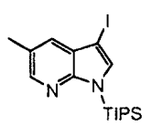
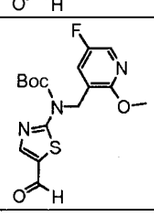
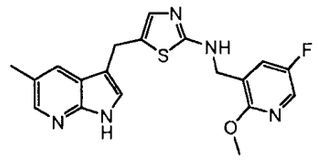
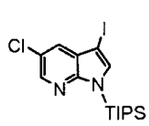
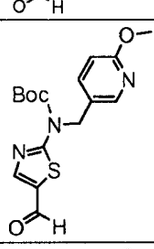
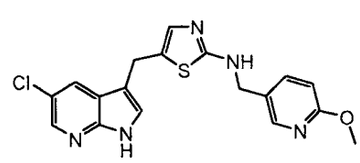
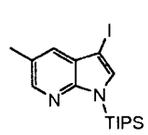
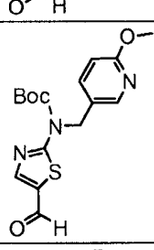
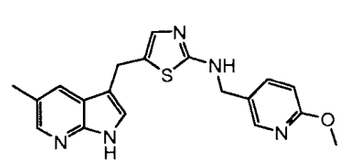
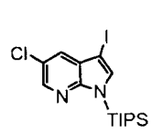
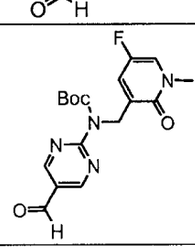
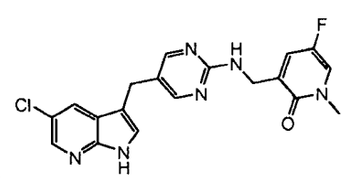
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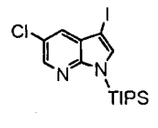
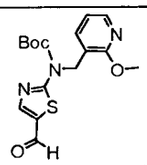
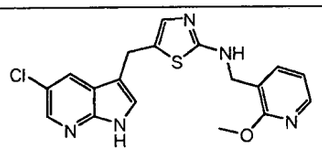
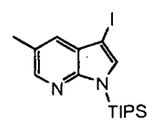
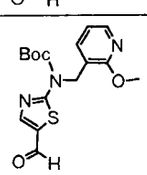
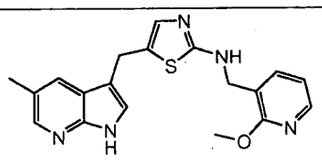
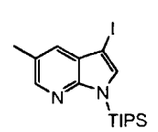
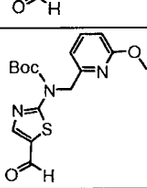
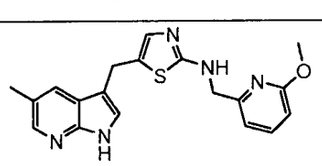
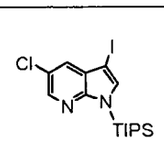
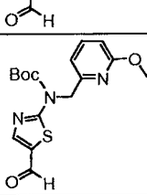
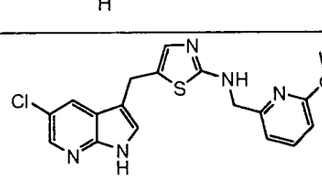
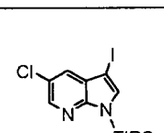
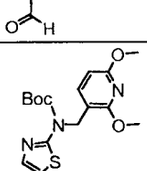
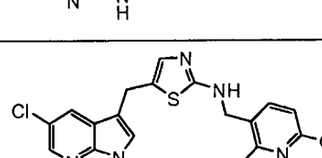
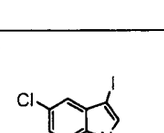
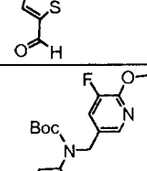
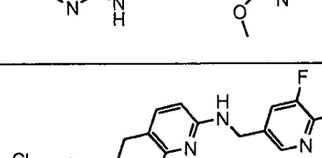
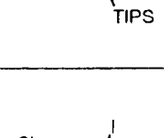
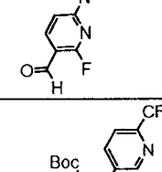
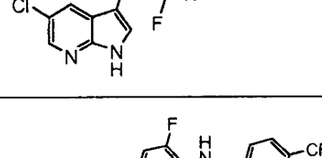
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P-2052				378.0

P-2057				360.95
P-2058				
P-2061				379.0
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P-2064				398.9
P-2065				
P-2067				361.85

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P-2070				398.2
P-2071				396.2
P-2072				379.0
P-2073				379.0
P-2075				381.9
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P-2143				
P-2144				

P-2145				
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P-2153				
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P-2155				365.9
P-2157				

P-2158				385.9
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P-2162				
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P-2172				435.8

Example 26: Compound forms and formulations

[0431] The compounds disclosed herein can be prepared in additional forms, such as polymorphs, salt forms and complexes. Such solid forms can further improve the biopharmaceutical properties, and can be further formulated to enhance biopharmaceutical properties. For example, compounds of the invention form acid addition salts such as hydrochloride or tosylate salts or form a complex with polyprotic acids, such as citric acid, preferably wherein the complex is substantially amorphous. Such an amorphous complex can also be processed with addition of a polymer, such as HPMCAS, that further stabilizes the amorphous form. The process can also include spray drying of the material.

Compound is dissolved in 400-500 mL of acetone and added with stirring and heat to 1 equivalent of citric acid dissolved in ethanol. The solution is spray dried to provide the dried complex. Addional material is formulated with addition of the compound/citrate complex to polymer in the same ratio of acetone/ethanol, for example using either HPMCAS or a mixture of Eudragit® L100-55 and Poloxamer 407. In one sample, components are combined in the weight ratios of 40-50% compound, 15-25% citric acid, 25-35% Eudragit® L100-55 and 1-10% Poloxamer 407. In one sample, components are combined in the weight ratios of 40-50% compound, 15-25% citric acid, and 30-40% HPMCAS. The amorphous nature of the resulting complex or formulation of the complex can be determined by X-Ray Powder Diffraction (XRPD), infra-red spectrometry, and differential scanning calorimetry. For example using a ShimadzuXRD-6000 X-ray powder diffractometer using Cu Kα radiation. The tube voltage and amperage are set to 40 kV and 40 mA, respectively. The divergence and scattering slits are set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation is detected by a NaI scintillation detector. A θ-2θ continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5° to 40° 2θ is used. A silicon standard is analyzed to check the instrument alignment. Data are collected and analyzed using XRD-6100/7000 v.5.0. Sample is prepared for analysis by placing it in an aluminum holder with silicon insert. The DSC is used to demonstrate that the complexes lack a characteristic transition and have completely melted before any free base crystalline transition, further supporting that these complexes are amorphous.

Example 27: Compound properties

[0432] While the inhibitory activity of the compounds on any of Fms, Flt-3 and Kit 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 metastatic 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.

[0433] 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. 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}.

[0434] 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}.

[0435] 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}.

[0436] Compounds are assessed in a variety of cell based assays. For example BCR-FMS/BaF3, BCR-KIT/BaF3, M-NFS-60, M-07e, and BAC1.2F5 cell proliferation assays are used to assess inhibitory acitivity of Fms or Kit and MV-4-11 cell proliferation assay is used to assess inhibitory activity in Flt-3. Reagent and assay conditions are as follows:

BCR-FMS/BaF3 and BCR-KIT/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.

M-NFS-60 cells (ATCC #CRL-1838):
Maintained in RPMI containing 10% FBS, 1% Hepes, 1% NaPyruvate, and 0.45% Glucose, supplemented with 62 ng/mL murine M-CSF.
Confluent cells are split 1:20 every 3-4 days.

M-07e cells (DSMZ #ACC 104):
Maintained in IMDM containing 10% FBS, supplemented with either 200 ng/mL human SCF or 75 ng/μL SCF (R&D Systems 255-SC).
Confluent cells are split 1:5 to 1:10 every 3-4 days.

BAC1.2F5 cells:
Maintained in Alpha-MEM containing 10% Newborn Calf Serum (Invitrogen #26010-074) supplemented with 36 ng/mL murine M-CSF.
Confluent cells are split 1:4 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.

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:

BCR-FMS/BaF3 and BCR-KIT/BaF3: resuspend in growth media + 1 mg/mL G418 (without WEHI/IL-3) to 2 X 10^5 cells/mL.

M-NFS-60: resuspend in growth media + 62 ng/mL murine M-CSF to 5 X 10^5 cells/mL.

M-07e: resuspend in growth media + 200 ng/mL human SCF to 5 X 10^5 cells/mL.

BAC1.2F5: resuspend in growth media + 36 ng/mL murine M-CSF to 1.4 X 10^5 cells/mL.

MV-4-11: resuspend in growth media + 10% FBS to 5 X 10^5 cells/mL.

The cells are plated (50 μL) in each well of a 96-well dish (Corning 3610) and incubated at 37 °C in 5% CO_2 overnight, cells plated to a final concentration of cells as follows:

BCR-FMS/BaF3 and BCR-KIT/BaF3: 10,000 cells per well.

M-NFS-60: 25,000 cells per well.

M-07e: 25,000 cells per well.

BAC1.2F5: 7,000 cells per well.

MV-4-11: 25,000 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.

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:

BCR-FMS/BaF3 and BCR-KIT/BaF3: 25 µL per well.

M-NFS-60: 25 µL per well.

M-07e: 40 µL per well.

BAC1.2F5: 50 µL per well.

MV-4-11: 40 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.

[0437] 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.

[0438] The following table indicates the Fms and Kit biochemical inhibitory activity and selectivity (Kit IC_{50}/FmsIC_{50}) and the BCR-FMS/BaF3 and BCR-KIT/BaF3 cell based inhibitory activity selectivity (Kit IC_{50}/FmsIC_{50}) for exemplary compounds according to the invention as indicated:

Compound number	Biochemical activity (IC_{50} µM)			BCR/BaF3 (IC_{50} µM)		
	Fms	Kit	selectivity	Fms	Kit	selectivity
P-1496	< 0.1			< 0.1	> 0.1	> 20
P-1554	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-1562	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-1622	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-1669				< 0.1	> 0.1	> 20
P-1679	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2001	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2003	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2004	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2008	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2013	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2019	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2028	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2029	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2030	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2031	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2032	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2037	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2038	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2043	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2045	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2048	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2049	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2052	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20

P-2057	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2061	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2062	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2063	< 0.1	< 0.1	< 20	< 0.1	> 0.1	> 20
P-2064	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2067	< 0.1	> 0.1	> 20			
P-2070	< 0.1	< 0.1	< 20	< 0.1	> 0.1	> 20
P-2071	< 0.1	> 0.1	> 20	> 0.1	> 0.1	> 20
P-2073	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2075	< 0.1	> 0.1	> 20			
P-2078	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2079	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2081	< 0.1	< 0.1	< 20	> 0.1	> 0.1	< 20
P-2082	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2088	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2097	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2103	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2118	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2131	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2139	< 0.1	> 0.1	> 20	> 0.1	> 0.1	< 20
P-2146	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2147	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2148	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2154	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2157	> 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2163	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2165	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2172	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2176	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2193	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2198	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2202	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20

[0439] The following table indicates the Fms and Flt-3 biochemical inhibitory activity and the BCR-FMS/BaF3 and MV-4-11 cell based inhibitory activity for exemplary compounds according to the invention that are approximately equipotent inhibitors of Fms/Flt-3 as indicated:

Compound number	Biochemical (IC_{50} μM)		Cell based (IC_{50} μM)	
	Fms	Flt-3	BCR/BaF3 (Fms)	MV-4-11 (Flt-3)
P-1644	< 0.1	< 0.1	< 0.1	
P-1646	< 0.1	< 0.1	< 0.1	
P-2003	< 0.1	< 0.1	< 0.1	> 0.1
P-2004	< 0.1	< 0.1	< 0.1	
P-2009	< 0.1	< 0.1	< 0.1	
P-2019	< 0.1	< 0.1	< 0.1	
P-2029	< 0.1	< 0.1	< 0.1	< 0.1
P-2030	< 0.1	< 0.1	< 0.1	< 0.1
P-2031	< 0.1	< 0.1	< 0.1	< 0.1
P-2032	< 0.1	< 0.1	< 0.1	< 0.1
P-2034	< 0.1	< 0.1	< 0.1	> 0.1

P-2037	< 0.1	< 0.1	< 0.1	> 0.1
P-2038	< 0.1	< 0.1	< 0.1	< 0.1
P-2044	< 0.1	> 0.1	< 0.1	< 0.1
P-2048	< 0.1	< 0.1	< 0.1	> 0.1
P-2057	< 0.1	< 0.1	< 0.1	< 0.1
P-2165	< 0.1	< 0.1	< 0.1	> 0.1

[0440] Compounds P-1554, P-2001, P-2003, P-2004, P-2019, P-2028, P-2029, P-2030, P-2031, P-2032, P-2037, P-2038, P-2045, P-2048, P-2049, P-2052, P-2057, P-2061, P-2063, P-2064, P-2070, P-2146, P-2147, P-2157, P-2165, P-2176, and P-2193 demonstrated an IC_{50} below 0.1 μM in the osteoclast differentiation assay.

[0441] 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.

[0442] 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.

[0443] 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-1554	H	H	M	M
P-1562	H	H	M	M
P-1622	H	M	M	M
P-1669	M	M	M	M
P-1679	M	L	L	L
P-2001	M	L	L	L
P-2003	H	M	L	L
P-2004	H	M	M	M
P-2019	H	M	M	L
P-2028	H	M	M	M
P-2029	H	M	M	M
P-2030	H	M	M	L
P-2031	M	L	L	L
P-2032	M	L	L	L
P-2037	M	L	L	L
P-2038	H	L	L	L
P-2043	H	M	M	M
P-2045	H	M	M	M
P-2048	M	L	L	L
P-2049	M	L	L	L
P-2052	H	L	L	L
P-2057	H	L	L	M
P-2061	H	M	M	L
P-2062	H	L	L	L
P-2064	H	M	L	L
P-2067	H	H	H	H
P-2071	M	L	L	L
P-2073	H	M	M	M
P-2075	H	M	L	M
P-2146	H	M	M	L
P-2165	L	L	L	L
P-2172	H	L	L	L
P-2193		L		
P-2198	M	L	L	L

[0444] 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.

[0445] 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.

[0446] 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-1562	> 10	> 10	< 5	> 10	5-10	5-10
P-1622	> 10	< 5	5-10	> 10	5-10	5-10
P-1669	> 10	> 10	< 5	> 10	5-10	
P-1679	> 10	< 5	< 5	> 10	> 10	
P-2001	> 10	< 5	5-10	> 10	5-10	5-10
P-2003	> 10	5-10	< 5	> 10	5-10	> 10
P-2004	> 10	5-10	< 5	5-10	< 5	5-10
P-2019	> 10	5-10	< 5	< 5	< 5	> 10
P-2028	> 10	> 10	< 5	> 10	< 5	< 5
P-2029	> 10	< 5	< 5	> 10	5-10	5-10
P-2030	> 10	< 5	< 5	> 10	5-10	> 10
P-2031	> 10	< 5	< 5	> 10	5-10	5-10
P-2032	5-10	< 5	< 5	> 10	> 10	> 10
P-2037	> 10	< 5	< 5	> 10	5-10	> 10
P-2038	> 10	> 10	5-10	> 10	> 10	> 10
P-2043	> 10	> 10	5-10	> 10	> 10	5-10
P-2045	> 10	5-10	> 10	> 10	5-10	> 10
P-2048	> 10	> 10	> 10	> 10	> 10	> 10
P-2049	> 10	5-10	5-10	> 10	5-10	> 10
P-2052	> 10	> 10	5-10	> 10	5-10	5-10
P-2057	> 10	5-10	5-10	> 10	> 10	> 10
P-2061	> 10	> 10	5-10	> 10	> 10	5-10
P-2062	> 10	< 5	< 5	> 10	5-10	5-10
P-2063	> 10	5-10	> 10	> 10	5-10	5-10
P-2064	> 10	> 10	5-10	> 10	> 10	> 10
P-2067	> 10	< 5	< 5	> 10	< 5	> 10
P-2071	> 10	> 10	5-10	> 10	5-10	5-10

P-2073	> 10	> 10	< 5	> 10	5-10	> 10
P-2075	5-10	< 5	< 5	> 10	< 5	5-10
P-2078	> 10	> 10	< 5	> 10	< 5	> 10
P-2079	> 10	5-10	5-10	> 10	< 5	5-10
P-2081	> 10	< 5	< 5	> 10	< 5	5-10
P-2082	> 10	< 5	< 5	> 10	< 5	< 5
P-2088	> 10	< 5	< 5	> 10	5-10	5-10
P-2097	> 10	< 5	< 5	> 10	5-10	5-10
P-2103	> 10	< 5	< 5	> 10	5-10	5-10
P-2118	> 10	< 5	5-10	> 10	5-10	> 10
P-2131	> 10	5-10	< 5	> 10	< 5	> 10
P-2139	> 10	> 10	5-10	> 10	5-10	> 10
P-2146	> 10	< 5	5-10	> 10	> 10	> 10
P-2147	> 10	< 5	> 10	> 10	5-10	5-10
P-2157	> 10	> 10	> 10	> 10	5-10	> 10
P-2165	> 10	> 10	> 10	> 10	> 10	> 10
P-2172	> 10	< 5	5-10	> 10	> 10	
P-2193	> 10	> 10	> 10	> 10	> 10	> 10
P-2198	> 10	< 5	5-10	> 10	< 5	

[0447] 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.

[0448] 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.

[0449] Additional features of the complex can be used to demonstrate improved properties, such as comparison of the intrinsic dissolution rate of a similarly prepared substantially amorphous citrate complex or formulation thereof as compared to that of a crystalline form of the compound or similar formulation thereof in simulated gastric fluid (SGF) without enzyme and in simulated intestinal fluid (SIF). A pellet of test sample is dissolved in the appropriate fluid, and the UV absorbance as a function of time is measured at 254 nm (SGF) or 310 nm (SIF) and plotted.

Example 28: *In vivo* model system testing

[0450] For *in vivo* testing, a suitable animal model system can be selected for use. For example, for multiple sclerosis, the rodent experimental allergic encephalomyelitis (EAE) system is commonly used. This system is described, for example, in Steinman, 1996, Cell 85:299-302 and Secor et al., 2000, J Exp. Med 5:813-821, which are incorporated herein by reference in their entireties. For rheumatoid arthritis (RA), the type II collagen-induced arthritis (CIA) small animal model of rheumatoid arthritis (RA) can be used for testing. This model is described, for example, in Wooley, et al. Current Rheumatology Reviews, 2008, 4 : 277–287, which is incorporated herein by reference in its entirety.

[0451] Similarly, other model systems can be used to evaluate compounds described herein. Numerous compounds described herein, including compounds of Formulas I, I', II, II', IIa, III, and

III' (e.g., P-1496, P-1622, P-1669, P-1679, P-2001, P-2028, P-2029, P-2030, P-2038, P-2043, P-2045, P-2048, P-2049, P-2052, P-2057, P-2061, P-2062, P-2063, P-2064, P-2067, P-2070, P-2071, P-2073, P-2075, P-2078, P-2088, P-2097, P-2103, P-2118, P-2139, P-2157, P-2165, P-2176, P-2193, P-1554, P-1562, P-2003, P-2004, P-2008, P-2013, P-2019, P-2031, P-2032, P-2037, P-2079, P-2081, P-2082, P-2131, P-2146, P-2147, P-2148, P-2154, P-2163, P-2172, P-2198, P-2202, P-1644, P-1646, P-1667, P-2003, P-2004, P-2009, P-2019, P-2029, P-2030, P-2031, P-2032, P-2034, P-2037, P-2038, P-2040, P-2041, P-2044, P-2047, P-2048, P-2050, P-2057 and P-2065; the compounds disclosed in paragraphs [0038], [0079], [0094], [0102], [0103], and [0104]; and the compounds described in the Examples), or compositions thereof, hydrates or solvates thereof, are tested in mice for the treatment of various diseases and conditions as described herein.

Collagen induced rheumatoid arthritis (RA) mouse model.

Methods: Intradermal injections with collagen-CFA, followed by a collagen boost by intraperitoneal (ip) injection on day 21 induces rheumatoid arthritis in a variety of mouse strains, especially the DBA/1 genotype used in this study (Brand et al., 2004; Wooley et al., 1981). Disease is quantified and recorded by clinical scores using a scale of 0–4 per paw. The score records the degree and extent of swelling and redness in each digit and joint and culminates in the absence of use of individual front or rear paws. Scores are accumulated per animal resulting in a maximum score of 16, which indicates that animals avoid the use of all paws. Groups were balanced for disease score at day 21 after the initial immunization when the average clinical score was 2.5 for all animals. Treatment was for 21 days with daily oral dosing with the following dosing groups: vehicle, and 10 mg/kg, 20 mg/kg and 50 mg/kg the compounds of the invention.

Results

[0452] Oral administration of the compounds of the invention inhibited the clinical disease development in the murine CIA model in a dose dependent fashion with significant responses at all doses tested (10, 20 and 50 mg/kg qd). Histopathological analysis of the joints showed inhibition of inflammation, bone resorption, cartilage damage and pannus formation by compounds of the invention treatment. The mechanism of action of compounds of the invention was confirmed by the decreased scores for macrophage and osteoclast-cells in the joints.

[0453] Daily oral administration of Fms kinase inhibitors described herein showed at all dose levels tested (10, 20 and 50 mg/kg) a rapid benefit as compared to the vehicle control, as evidenced by decreased clinical scores, reflecting less swelling and redness of limbs. This clinical benefit was confirmed by decreased histopathological scores for inflammation, cartilage damage, pannus formation and bone destruction. Scores for both macrophage and osteoclast-cells were decreased in

the joint tissues confirming that the mode of action of the compounds described herein is by inhibiting the Fms receptor tyrosine kinase, which is crucial for the proliferation and differentiation of these cell lineages. Plasma concentrations of the dose groups drawn at the 2 hr time point after dosing showed a clear dose proportional response.

[0454] 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.

[0455] 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.

[0456] 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.

[0457] 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.

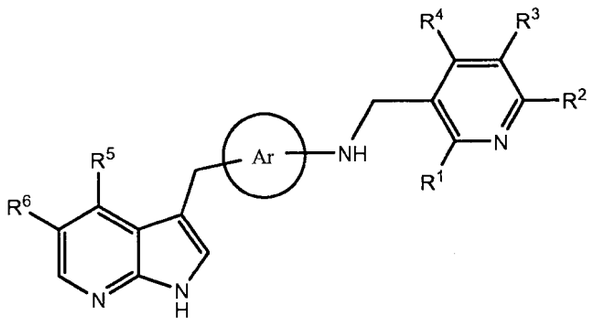
[0458] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0459] 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',

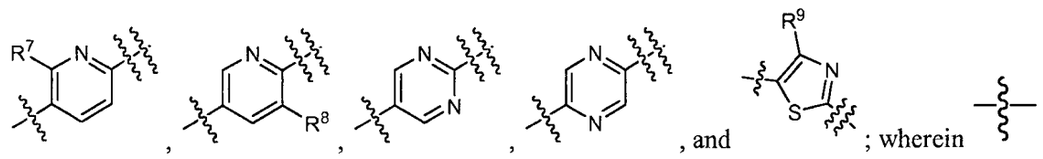


Formula I'

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

wherein:

Ar is selected from the group consisting of:



; wherein indicates the point of attachment of Ar to $-CH_2-$ of Formula I and wherein  indicates the point of attachment of Ar to -NH- of Formula I;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of –H, halogen, lower alkyl, halogen substituted lower alkyl, halogen substituted lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, and $-N(H)-S(O)_2-R^{43}$, provided that at least two of R^1, R^2, R^3 and R^4 are –H and one of R^1, R^2, R^3 and R^4 is other than hydrogen, wherein:

R^{40} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{41}, R^{42} and R^{43} are lower alkyl;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, and $-N(H)-S(O)_2-R^{12}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is H, halogen or lower alkyl;

R^8 is H, halogen or lower alkoxy;

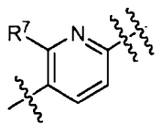
R^9 is H or halogen;

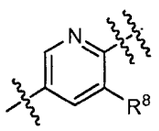
R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH_3, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

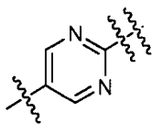
R^{11} and R^{14} are independently hydrogen or lower alkyl; and

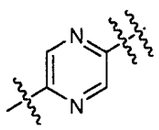
R^{12} and R^{15} are each independently lower alkyl,

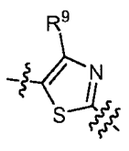
with the proviso that the compound is other than those set forth in Table 1.

2. The compound of claim **1**, wherein Ar is  .

3. The compound of claim **1**, wherein Ar is  .

4. The compound of claim **1**, wherein Ar is  .

5. The compound of claim **1**, wherein Ar is  .

6. The compound of claim **1**, wherein Ar is  .

7. The compound of any of claims **1-6**, wherein:

i) R^1, R^3 and R^4 are H and R^2 is halogen; or

ii) R^1, R^2 and R^3 are -H and R^4 is halo substituted lower alkyl; or

iii) R^1 and R^4 are –H and R^2 is lower alkoxy; or

iv) R^3 is halogen; or

v) R^2 and R^4 are -H, R^1 is lower alkoxy and R^3 is halogen.

8. The compound of claim **7**, wherein

i) R^1, R^2 and R^3 are -H and R^4 is CF_3; or

ii) R^1 and R^4 are –H and R^2 is $–OCH_3$; or

iii) R^3 is F; or

iv) R^2 and R^4 are -H, R^1 is OCH_3 and R^3 is F.

9. The compound of any of claims **1-8**, wherein R^5 is -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and -N(H)-$S(O)_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl

10. The compound of any of claims **1-8**, wherein R^6 is selected from the group consisting of H, halo, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl.

11. The compound of claim **10**, wherein R^6 is halo, lower alkyl or fluoro substituted lower alkyl.

12. The compound of any of claims **1, 2** and **7-9**, wherein R^7 is H, halogen or lower alkyl.

13. The compound of claim **12**, wherein R^7 is H, -F, -Cl, Br or $–CH_3$.

14. The compound of any of claims **1**, **3** and **7-9**, wherein R^8 is H, halogen or lower alkoxy.

15. The compound of claim **14**, wherein R^8 is H, -F, -Cl, Br or $–OCH_3$.

16. The compound of claim **1, 4** and **7-9**, wherein R^9 is H or halogen.

17. The compound of claim **16**, wherein R^9 is -H or -Cl

18. The compound of claim **1**, wherein:

R^1, R^3 and R^4 are –H, and R^2 is -F, -Cl or -Br; or R^1, R^2 and R^3 are -H and R^4 is $-CF_3$; or R^1 and R^4 are -H, R^2 is $-O-CH_3$, and R^3 is -F; or R^2 and R^4 are -H, R^1 is $-O-CH_3$, and R^3 is -F;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, and

-N(H)-S(O)$_2$-R^{12}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -S(O)$_2$-R^{15}, -S(O)$_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, and -N(H)-S(O)$_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is -H, -F, -Cl, or -CH$_3$;

R^8 is -H, -F, -CH$_3$, or -O-CH$_3$;

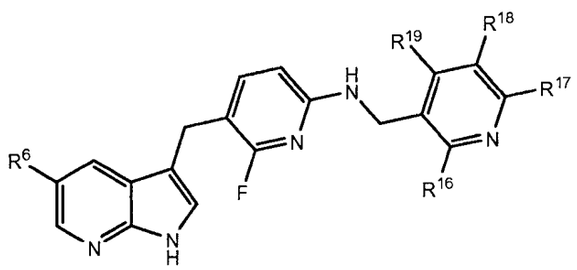
R^9 is -H or -Cl;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with -O-CH$_3$, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

R^{12} and R^{15} are each independently lower alkyl.

19. The compound of claim **1**, having Formula II':



Formula II'

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

wherein:

R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from the group consisting of H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-S(O)$_2$-R^{23}, provided that at least two of R^{16}, R^{17}, R^{18} and R^{19} are -H;

R^{20} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{21} is lower alkyl;

R^{22} is lower alkyl; and

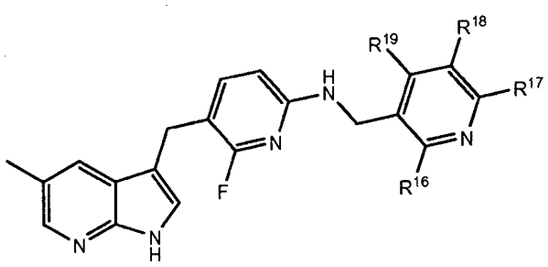
R^{23} is lower alkyl.

20. The compound of claim **19**, wherein R^6 is selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -S(O)$_2$-R^{15}, -S(O)$_2$-N(H)-R^{14},

-N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl.

21. The compound of claim **20**, wherein R^6 is F, Cl, Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}. -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} or -N(H)-$S(O)_2$-R^{15}.

22. The compound of claim **19**, having Formula II:

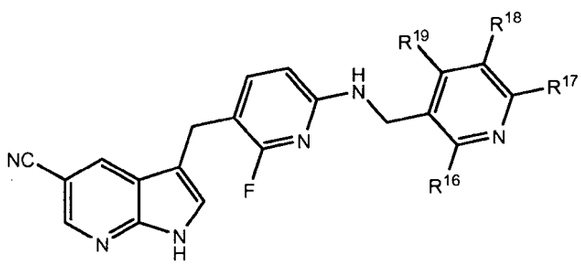


Formula II.

23. The compound of any of claims **19-22**, wherein R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, and -N(H)-$S(O)_2$-R^{23}.

24. The compound of any of claims **23**, wherein R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl.

25. The compound of claim **19**, having Formula IIa:



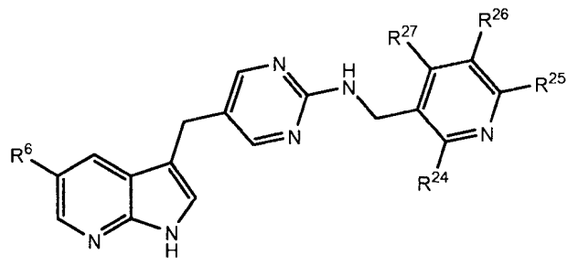
Formula IIa.

26. The compound of claim **25**, wherein R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl,

methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, and -N(H)-$S(O)_2$-R^{23}.

27. The compound of claim **26**, wherein R^{16}, R^{17}, R^{18} and R^{19} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl.

28. The compound of claim **1**, having Formula III':



Formula III'

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

wherein:

R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from the group consisting of -H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, lower alkoxy, alkoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -$S(O)_2$-N(H)-R^{30}, -N(H)-R^{30}, -$N(R^{30})_2$, and -N(H)-$S(O)_2$-R^{31}, provided that at least two of R^{24}, R^{25}, R^{26} and R^{27} are -H;

R^{28} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{29} is lower alkyl;

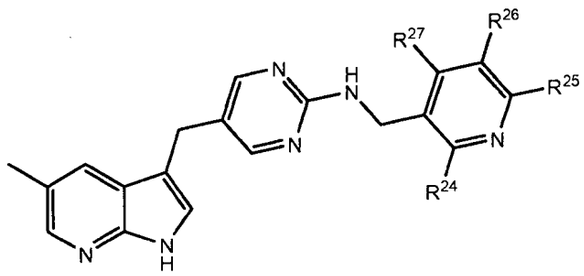
R^{30} is lower alkyl; and

R^{31} is lower alkyl.

29. The compound of claim **28**, wherein R^6 is selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}; -N(H)-C(O)-R^{15}, and -N(H)-$S(O)_2$-R^{15}, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl.

30. The compound of claim **29**, wherein wherein R^6 is F, Cl, Br, lower alkyl, fluoro substituted lower alkyl, lower alkenyl, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}. -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} or -N(H)-$S(O)_2$-R^{15}.

31. The compound of claim **28**, having Formula III:



Formula III.

32. The compound of any of claims 28-31, wherein R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, methoxy substituted lower alkyl, cycloalkylamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, and -N(H)-$S(O)_2$-R^{23}.

33. The compound of claim **32**, wherein R^{24}, R^{25}, R^{26} and R^{27} are each independently selected from H, halogen, lower alkyl, lower alkoxy, halo substituted lower alkyl, -OR^{20}, or alkoxy substituted lower alkyl.

34. A compound selected from the group consisting of:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-dimethoxy-pyridin-3-ylmethyl)-amine (**P-1496**),
[6-Fluoro-5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1622**),
N-(3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-acetamide (**P-1669**),
N-(3-{6-[(6-Chloro-pyridin-3-ylmethyl)-amino]-2-fluoro-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanesulfonamide (**P-1679**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2001**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2028**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2030**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-

pyridin-3-ylmethyl)-amine (**P-2043**),
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2045**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2049**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-2052**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2057**),
(5-Fluoro-2-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2061**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2062**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2063**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amine (**P-2064**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2067**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2070**),
(5-Fluoro-2-methoxy-pyridin-4-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2071**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2073**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(2-methyl-pyridin-4-ylmethyl)-amine (**P-2075**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2078**),
(6-Chloro-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2088**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2097**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-3-ylmethyl)-amine (**P-2103**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-pyridin-4-ylmethyl)-amine (**P-2118**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2139**),
3-{[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-ylamino]-methyl}-5-fluoro-1-methyl-1H-pyridin-2-one (**P-2157**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-2176**),
3-{2-Fluoro-6-[(5-fluoro-2-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-2193**),
5-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]pyridin-2-amine **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-methoxy-3-pyridyl)methylamino]-3-pyridyl]methyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-2204),**
6-chloro-N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-5-[(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyridin-2-amine **(P-2205),**
6-fluoro-N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-5-[[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methyl]pyridin-2-amine **(P-2206)** and
a salt, prodrug, tautomer, or stereoisomer thereof.

35. A compound selected from the group consisting of:
(6-Methoxy-pyridin-3-ylmethyl)-[3-methyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1554**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-1562**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine (**P-2004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,4-difluoro-benzyl)-amine (**P-2008**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-methyl-benzyl)-amine (**P-2013**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),

[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),
(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),
(6-Methyl-pyridin-2-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2079**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-2081**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-pyrrolidin-1-yl-pyridin-2-ylmethyl)-amine (**P-2082**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-methyl-pyridin-2-ylmethyl)-amine (**P-2131**),
[3-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2146**),
[3-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2147**),
(2-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-2148**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2154**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine (**P-2163**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2172**),
Ethanesulfonic acid (2-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2198**),
Ethanesulfonic acid (3-fluoro-5-{[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-2202**), and
any salt, prodrug, tautomer, or stereoisomer thereof.

36. A compound selected from the group consisting of:
(6-Trifluoromethyl-pyridin-3-ylmethyl)-[5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1644**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-1646**),

[5-(5-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-1667**),
(6-Chloro-pyridin-3-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2003**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-fluoro-pyridin-3-ylmethyl)-amine (**P-2004**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-5-trifluoromethyl-benzyl)-amine (**P-2009**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2019**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2029**),
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2030**),
[6-Fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-2031**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2032**),
(2-Chloro-benzyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2034**),
(4-Chloro-benzyl)-[6-fluoro-5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2037**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-2038**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2040**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2041**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2044**),
(5-Chloro-pyridin-2-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2047**),
(5-Fluoro-6-methoxy-pyridin-3-ylmethyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2048**),
(4-Chloro-benzyl)-[6-fluoro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-2050**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-

pyrimidin-2-yl]-amine (**P-2057**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-6-methoxy-pyridin-3-ylmethyl)-amine (**P-2165**), and
any salt, prodrug, tautomer, or stereoisomer thereof.

37. A composition comprising a compound of any of claims **1-36** and a pharmaceutically acceptable excipient or carrier.

38. A kit comprising a compound of any of claims **1-36** or a composition of claim **37**.

39. A compound of any of claims **1-36** for use as a medicament.

40. A method for treating a subject suffering from or at risk of a disease or condition, said method comprising administering to the subject in need thereof an effective amount of a compound of any of claims **1-36**, wherein the disease or condition is selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, and renal hypertrophy, metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors and acute myeloid leukemia.

41. The method of claim **40**, wherein the disease or condition is selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, systemic lupus erythematosus, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, and renal hypertrophy.

42. The method of claim **40**, wherein the disease or condition is selected from the group consisting of metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis.

43. The method of claim **40**, wherein the disease or condition is acute myeloid leukemia.

44. A method for treating a subject suffering from or at risk of a disease or condition, said method comprising administering to the subject in need thereof an effective amount of a compound of claim **34**, wherein the disease or condition is selected from the group consisting of multiple sclerosis, glioblastoma, Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, systemic lupus erythematosus, glomerulonephritis,

interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, and renal hypertrophy.

45. A method of for treating a subject suffering from or at risk of a disease or condition, said method comprising administering to the subject in need thereof an effective amount of a compound of claim **35**, wherein the disease or condition is selected from the group consisting of metastatic breast cancer, prostate cancer, multiple myeloma, melanoma, acute myeloid leukemia, brain metastases, neurofibromatosis, gastrointestinal stromal tumors, rheumatoid arthritis, and multiple sclerosis.

46. A method of for treating a subject suffering from or at risk of a disease or condition, said method comprising administering to the subject in need thereof an effective amount of a compound of claim **36**, wherein the disease or condition is acute myeloid leukemia.

47. A pharmaceutical composition comprising a compound of any of claims **1-36** and another drug, wherein the other drug is selected from:

i) an alkylating agent selected from adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan;

ii) an antibiotic selected from bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite, including, but not limited to, azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate;

iii) an immunotherapy agent selected from alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene;

iv) a taxan selected from DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel;

v) a retinoid selected from alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin;

vi) an alkaloid selected from etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine;

vii) an antiangiogenic agent selected from AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide;

viii) a topoisomerase inhibitor selected from amsacrine, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin;

ix) a kinase inhibitor selected from erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib;

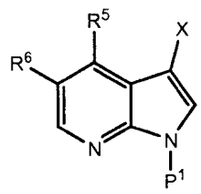
x) a targeted signal transduction inhibitor selected from bortezomib, geldanamycin, and rapamycin;

xi) a biological response modifier selected from imiquimod, interferon-α, and interleukin-2; and

xii) a chemotherapeutic agent selected from 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate (E7389), ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, tiazofurin, mTOR inhibitors (e.g. temsirolimus, everolimus, deforolimus), PI3K inhibitors (e.g. BEZ235, GDC-0941, XL147, XL765), Cdk4 inhibitors (e.g. PD-332991), Akt inhibitors, Hsp90 inhibitors (e.g. tanespimycin) and farnesyltransferase inhibitors (e.g. tipifarnib).

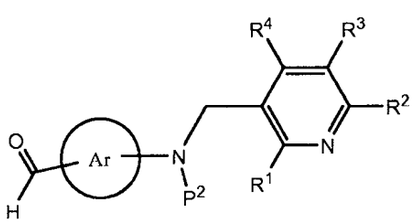
48. A method for preparing a compound of Formula I according to claim **1**, said method comprising:

contacting a compound of Formula IV:



Formula IV

with a compound of Formula V:



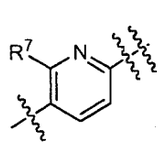
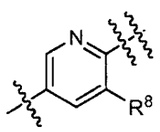
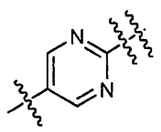
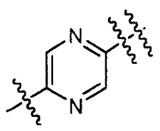
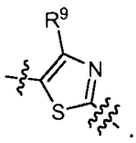
Formula V

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

P^1 and P^2 are each independently an amino protecting group;

X is H or halogen;

Ar is selected from the group consisting of:





, and

; wherein

indicates the point of attachment of Ar to $-CH_2-$ of Formula I and wherein

indicates the point of attachment of Ar to -NH- of Formula I;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of –H, lower alkyl, halogen substituted lower alkyl, alkoxy substituted lower alkyl, cycloalkylamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, and $-N(H)-S(O)_2-R^{43}$, provided that at least two of R^1, R^2, R^3 and R^4 are –H and one of R^1, R^2, R^3 and R^4 is other than hydrogen, wherein:

R^{40} is lower alkyl, fluoro substituted lower alkyl, methoxy substituted lower alkyl, or cycloalkyl;

R^{41}, R^{42} and R^{43} are lower alkyl;

R^5 is selected from the group consisting of -H, -F, -Cl, -Br, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, and $-N(H)-S(O)_2-R^{12}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^6 is selected from the group consisting of H, halogen, lower alkyl, halogen substituted alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl, pyrazolyl, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, and $-N(H)-S(O)_2-R^{15}$, wherein pyrazolyl is optionally substituted with lower alkyl or heterocycloalkyl;

R^7 is H, halogen or lower alkyl;

R^8 is H, halogen, lower alkyl or lower alkoxy;

R^9 is H or halogen;

R^{10} and R^{13} are independently -H, lower alkyl, lower alkyl substituted with $-O-CH_3$, lower alkyl substituted with di-alklylamine, or lower alkyl substituted with heterocycloalkyl;

R^{11} and R^{14} are independently hydrogen or lower alkyl; and

R^{12} and R^{15} are each independently lower alkyl.

49. Use of a compound of claim **34** to selectively modulate the activity of Fms kinase.

50. Use of a compound of claim **35** to modulate the activity of Fms/Kit kinases.

51. Use of a compound of claim **36** to modulate the activity of Fms/Flt kinases.

52. A composition comprising a compound of any of claims **34-36** and a pharmaceutically acceptable excipient or carrier.

13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/55519

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/519 (2010.01)
USPC - 514/265.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/265.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/158; 514/264.1; 514/415; 514/438; 514/443-444; 514/461; 514/466 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB
Google: Scholar/patents: compounds modulating c-kit pyrrolo pyridine indole thiazole fms flt kinase inhibitors pyrimidine myeloid leukemia multiple sclerosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2009/0076046 A1 (ZHANG et al.) 19 March 2009 (19.03.2009) para [0012]-[0027], [0039], [0046], [0083], [0738], [0742], [0749], [0759]-[0760], [1049], [1056]; Schemes 15-16	1-8, 18-36, 44-46, 48-52

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 2010 (28.12.2010)	14 JAN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/55519

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-17, 37-43 and 47
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

COMPUESTOS Y MÉTODOS PARA LA MODULACIÓN DE CINASAS, E INDICACIONES PARA ELLO

CAMPO DE LA INVENCIÓN

[0001] Se dan a conocer compuestos novedosos y usos de los mismos. En ciertas modalidades, los compuestos dados a conocer son inhibidores de cinasas Fms. En ciertas modalidades, los compuestos dados a conocer son inhibidores de cinasas Fms y Kit. En ciertas modalidades, los compuestos dados a conocer son inhibidores de cinasas Fms y Flt-3.

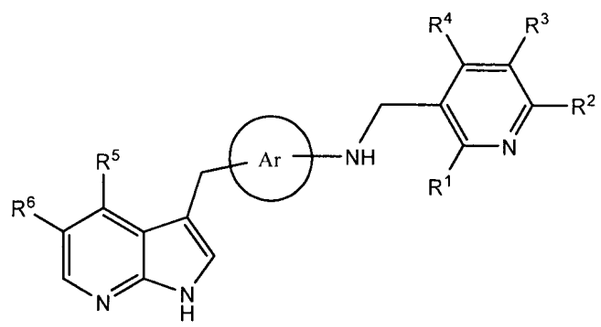
SUMARIO DE LA INVENCIÓN

[0002] En ciertos aspectos y modalidades dados a conocer en este documento, se proporcionan compuestos, así como diversas sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, formas de los mismos y usos de los mismos. En algunas modalidades, los compuestos son de la Fórmula I', Fórmula I, Fórmula II', Fórmula II, Fórmula IIa, Fórmula III' o Fórmula III como se describe a continuación. En ciertas modalidades, los compuestos inhiben la proteína cinasa Fms de manera selectiva en relación con otras proteína cinasas, incluyendo las proteína cinasas Kit y Flt-3. En ciertas modalidades, los compuestos inhiben tanto a la proteína cinasa Fms como a la proteína cinasa Kit. En ciertas modalidades, los compuestos inhiben tanto a la proteína cinasa Fms como a la proteína cinasa Flt-3. En ciertas modalidades, los compuestos inhiben a cada una de proteína cinasa Fms, proteína cinasa Kit y proteína cinasa Flt-3.

[0003] También se contemplan, de acuerdo con la presente invención, métodos para el uso de los compuestos para tratar enfermedades y padecimientos asociados con la regulación de la actividad de cualquiera de proteína cinasa Fms, proteína cinasa Kit, y proteína cinasa Flt-3, incluyendo cualquier mutación de estas cinasas. De esta manera, se proporciona el uso de compuestos para métodos terapéuticos que implican la modulación de proteína cinasas. En ciertas modalidades, los compuestos se usan para métodos terapéuticos que implican la modulación de cinasa Fms, cinasas Fms y Kit, cinasas Fms y Flt-3, o cinasas Fms, Kit y Flt-3, incluyendo el tratamiento de una diversidad de indicaciones, incluyendo, pero sin limitarse a, artritis reumatoide, osteoartritis, osteoporosis, osteólisis peri-prostética, esclerosis sistémica, trastornos desmielinizantes, esclerosis múltiple, síndrome de Charcot Marie Tooth, esclerosis lateral amiotrófica, enfermedad de Alzheimer, enfermedad de

Parkinson, colitis ulcerativa, enfermedad de Crohn, púrpura trombocitopénica inmune, aterosclerosis, lupus eritematoso sistémico, preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de mama metastásico , cáncer de próstata, cáncer pancreático, cáncer pulmonar, cáncer ovárico, gliomas, glioblastomas, neurofibromatosis, metástasis óseas osteolíticas, metástasis cerebrales, tumores de estroma gastrointestinal, y tumores de células gigantes.

[0004] En un primer aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula I':

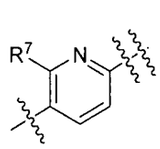


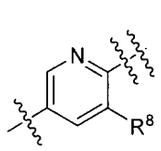
Fórmula I'

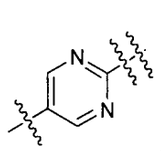
o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

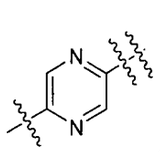
en donde:

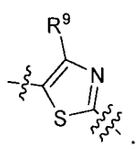
Ar se selecciona del grupo que consiste de:



,


,


,


, y


; en donde

indica el punto de unión de Ar a $-CH_2-$ de la Fórmula I' y en donde

indica el punto de unión de Ar a -NH- de la Fórmula I';

R^1, R^2, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, halógeno, alquilo inferior, alquilo inferior sustituido con halógeno, alcoxi inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{40}, -$S(O)_2$-R^{41}, -$S(O)_2$-N(H)-R^{42}, -N(H)-R^{42}, -$N(R^{42})_2$, y -N(H)-$S(O)_2$-R^{43}, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean –H y uno de R^1, R^2, R^3 y R^4 sea diferente a hidrógeno, en donde:

R^{40} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{41}, R^{42} y R^{43} son alquilo inferior;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, y -N(H)-$S(O)_2$-R^{12}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es H, halógeno, o alquilo inferior;

R^8 es H, halógeno, o alcoxi inferior;

R^9 es H o halógeno;

R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con -O-CH_3, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

R^{12} y R^{15} son cada uno independientemente alquilo inferior,

con la condición de que el compuesto sea diferente a aquel establecido en la Tabla 1.

[0005] En algunas modalidades, R^1, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, alcoxi inferior, halógeno, alquilo inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{40}, -$S(O)_2$-R^{41}, -$S(O)_2$-N(H)-R^{42}, -N(H)-R^{42}, -$N(R^{42})_2$, y -N(H)-$S(O)_2$-R^{43}, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean -H y R^2 sea -F, -Cl o -Br; o R^1, R^2 y R^3 son -H y R^4 es -CF_3; o R^1 y R^4 son -H, R^2 es -O-CH_3, y R^3 es -F; o R^2 y R^4 son -H, R^1 es -O-CH_3, y R^3 es -F;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{10}, -C(O)-N(H)-R^{11}, -C(O)-O-R^{11}, -$S(O)_2$-R^{12}, -$S(O)_2$-N(H)-R^{11}, -N(H)-C(O)-R^{12}, y -N(H)-$S(O)_2$-R^{12}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es -H, -F, -Cl, o $-CH_3$;

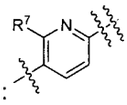
R^8 es -H, -F, $-CH_3$, o $-O-CH_3$;

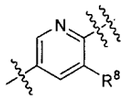
R^9 es -H o -Cl;

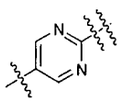
R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con $-O-CH_3$, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

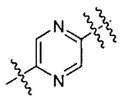
R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

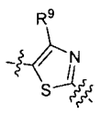
R^{12} y R^{15} son independientemente alquilo inferior.

[0006] En algunas modalidades, Ar es:  , en donde R^7 es como se define en este documento.

[0007] En algunas modalidades, Ar es  , en donde R^8 es como se define en este documento.

[0008] En algunas modalidades, Ar es  .

[0009] En algunas modalidades, Ar es  .

[0010] En algunas modalidades,  , en donde R^9 es como se define en este documento.

[0011] En algunas modalidades, R^1, R^3 y R^4 son H y R^2 es halógeno. En otras modalidades, R^1, R^2 y R^3 son –H, y R^4 es alquilo inferior halo sustituido. En otras modalidades, R^1 y R^4 son –H y R^2 es alcoxi inferior. En algunas modalidades, R^3 es halógeno. Todavía en otras modalidades, R^2 y R^4 son -H, R^1 es alcoxi inferior y R^3 es halógeno. En ciertos casos, i) R^1, R^2 y R^3 son -H y R^4 es CF_3; o ii) R^1 y R^4 son –H y R^2 es $-OCH_3$; o iii) R^3 es F; o iv) R^2 y R^4 son -H, R^1 es OCH_3 y R^3 es F. Las variables R^5, R^6 y Ar son como se define en este documento.

[0012] En algunas modalidades de los compuestos de la Fórmula I', R^5 es -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$,

y -N(H)-S(O)$_2$-R^{12}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. En ciertos casos, R^5 es H. Todas las otras variables son como se define en este documento.

[0013] En algunas modalidades de los compuestos de la Fórmula I', R^5 es -H. **En algunas modalidades, R^5 es -H y R^6 es -H, -F, -Cl, -CH$_3$, -CF$_3$, -CN, -O-CH$_3$, -S(O)$_2$-CH$_3$, -C(O)-NH-CH$_3$, -C(O)-O-CH$_3$, -NHC(O)CH$_3$, -NHS(O)$_2$CH$_3$, o ciclopropilo. Todas las otras variables son como se define en este documento.**

[0014] En algunas modalidades de los compuestos de la Fórmula I', R^6 se selecciona del grupo que consiste de H, halo, alquilo inferior, alcoxi inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -S(O)$_2$-R^{15}, -S(O)$_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-S(O)$_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. En ciertos casos, R^6 es halo, alquilo inferior o alquilo inferior sustituido con flúor. Todas las otras variables son como se define en este documento.

[0015] En algunas modalidades de los compuestos de la Fórmula I', R^6 es -H. En algunas modalidades, R^6 es -H y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH$_3$, o fenilo. En otras modalidades, R^6 es halo, alquilo inferior, alcoxi inferior, o alquilo inferior sustituido con flúor. Todavía en otras modalidades, R^6 es halógeno, metilo, metoxi, trifluorometilo, o CN. Todas las otras variables son como se define en este documento.

[0016] En algunas modalidades de los compuestos de la Fórmula I', R^7 es H, halógeno o alquilo inferior. En otras modalidades, R^7 es H, -F, -Cl, Br o –CH$_3$. Todas las otras variables son como se define en este documento.

[0017] En algunas modalidades de los compuestos de la Fórmula I', R^8 es H, halógeno o alcoxi inferior. En otras modalidades, R^8 es H, -F, -Cl, Br o –OCH$_3$. Todas las otras variables son como se define en este documento.

[0018] En algunas modalidades de los compuestos de la Fórmula I', R^9 es H o halógeno. En otras modalidades, R^9 es -H o –Cl. Todas las otras variables son como se define en este documento.

[0019] En algunas modalidades de los compuestos de la Fórmula I', R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; y R^5 es -H. En algunas modalidades, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; R^5 es -H; y R^6 es -H, -F, -Cl, -CH$_3$, -CF$_3$, -CN, -O-CH$_3$, -S(O)$_2$-CH$_3$, -C(O)-NH-CH$_3$, -C(O)-O-CH$_3$, -NHC(O)CH$_3$, -NHS(O)$_2$CH$_3$, o ciclopropilo. Todas las otras variables son como se define en este documento.

[0020] En algunas modalidades de los compuestos de la Fórmula I', R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; y R^6 es -H. En algunas modalidades, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH_3, o fenilo. Todas las otras variables son como se define en este documento.

[0021] En algunas modalidades de los compuestos de la Fórmula I', R^1, R^2 y R^3 son -H; y R^4 es -CF_3; y R^5 es -H. En algunas modalidades, R^1, R^2 y R^3 son -H; y R^4 es -CF_3; R^5 es -H; y R^6 es -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -$NHS(O)_2CH_3$, o ciclopropilo. Todas las otras variables son como se define en este documento.

[0022] En algunas modalidades de los compuestos de la Fórmula I', R^1, R^2 y R^3 son -H; y R^4 es -CF_3; y R^6 es -H. En algunas modalidades, R^1, R^2 y R^3 son -H; y R^4 es -CF_3; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH_3, o fenilo. Todas las otras variables son como se define en este documento.

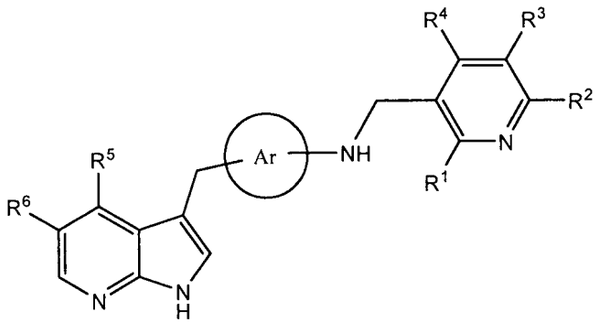
[0023] En algunas modalidades de los compuestos de la Fórmula I', R^1 y R^4 son -H; R^2 es -O-CH_3; R^3 es -F; y R^5 es -H. En algunas modalidades, R^1 y R^4 son -H; R^2 es -O-CH_3; R^3 es -F; R^5 es -H; y R^6 es -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -$NHS(O)_2CH_3$, o ciclopropilo. Todas las otras variables son como se define en este documento.

[0024] En algunas modalidades de los compuestos de la Fórmula I', R^1 y R^4 son -H; R^2 es -O-CH_3; R^3 es -F; y R^6 es -H. En algunas modalidades, R^1 y R^4 son -H; R^2 es -O-CH_3; R^3 es -F; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH_3, o fenilo. Todas las otras variables son como se define en este documento.

[0025] En algunas modalidades de los compuestos de la Fórmula I', R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; y R^5 es -H. En algunas modalidades, R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; R^5 es -H; y R^6 es -H, -F, -Cl, -CH_3, -CF_3, -CN, -O-CH_3, -$S(O)_2$-CH_3, -C(O)-NH-CH_3, -C(O)-O-CH_3, -NHC(O)CH_3, -$NHS(O)_2CH_3$, o ciclopropilo. Todas las otras variables son como se define en este documento.

[0026] En algunas modalidades de los compuestos de la Fórmula I', R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; y R^6 es -H. En algunas modalidades, R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH_3, o fenilo. Todas las otras variables son como se define en este documento.

[0027] En otro aspecto, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula I:

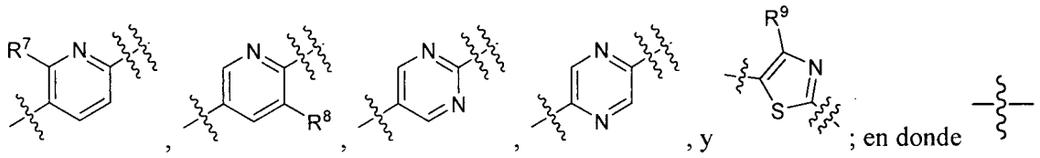


Fórmula I

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

Ar se selecciona del grupo que consiste de:



; en donde indica el punto de unión de Ar a $-CH_2-$ de la Fórmula I y en donde  indica el punto de unión de Ar a -NH- de la Fórmula I;

R^1, R^3 y R^4 son -H y R^2 es -F, -Cl o -Br; o R^1, R^2 y R^3 son -H y R^4 es $-CF_3$; o R^1 y R^4 son -H, R^2 es $-O-CH_3$, y R^3 es -F; o R^2 y R^4 son -H, R^1 es $-O-CH_3$, y R^3 es -F;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, y $-N(H)-S(O)_2-R^{15}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es -H, -F, -Cl, o $-CH_3$;

R^8 es -H, -F, $-CH_3$, o $-O-CH_3$;

R^9 es -H o -Cl;

R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con $-O-CH_3$, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

R^{12} y R^{15} son independientemente alquilo inferior.

[0028] En algunas modalidades de los compuestos de la Fórmula I, R^5 es -H. En algunas modalidades, R^5 es -H y R^6 es -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, o ciclopropilo.

[0029] En algunas modalidades de los compuestos de la Fórmula I, R^6 es -H. En algunas modalidades, R^6 es -H y R^5 es -H, -Cl, -CN, -C≡CH, $-O-CH_3$, o fenilo.

[0030] En algunas modalidades de los compuestos de la Fórmula I, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; y R^5 es -H. En algunas modalidades, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; R^5 es -H; y R^6 es -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, o ciclopropilo.

[0031] En algunas modalidades de los compuestos de la Fórmula I, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; y R^6 es -H. En algunas modalidades, R^1, R^3 y R^4 son -H; R^2 es -F, -Cl o -Br; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, $-O-CH_3$, o fenilo.

[0032] En algunas modalidades de los compuestos de la Fórmula I, R^1, R^2 y R^3 son -H; y R^4 es $-CF_3$; y R^5 es -H. En algunas modalidades, R^1, R^2 y R^3 son -H; y R^4 es $-CF_3$; R^5 es -H; y R^6 es -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, o ciclopropilo.

[0033] En algunas modalidades de los compuestos de la Fórmula I, R^1, R^2 y R^3 son -H; y R^4 es $-CF_3$; y R^6 es -H. En algunas modalidades, R^1, R^2 y R^3 son -H; y R^4 es $-CF_3$; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, $-O-CH_3$, o fenilo.

[0034] En algunas modalidades de los compuestos de la Fórmula I, R^1 y R^4 son -H; R^2 es $-O-CH_3$; R^3 es -F; y R^5 es -H. En algunas modalidades, R^1 y R^4 son -H; R^2 es $-O-CH_3$; R^3 es -F; R^5 es -H; y R^6 es -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, o ciclopropilo.

[0035] En algunas modalidades de los compuestos de la Fórmula I, R^1 y R^4 son -H; R^2 es $-O-CH_3$; R^3 es -F; y R^6 es -H. En algunas modalidades, R^1 y R^4 son -H; R^2 es $-O-CH_3$; R^3 es -F; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, $-O-CH_3$, o fenilo.

[0036] En algunas modalidades de los compuestos de la Fórmula I, R^2 y R^4 son -H; R^1 es $-O-CH_3$; R^3 es -F; y R^5 es -H. En algunas modalidades, R^2 y R^4 son -H; R^1 es $-O-CH_3$; R^3 es -F; R^5 es -H; y R^6 es -H, -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-O-CH_3$, $-S(O)_2-CH_3$, $-C(O)-NH-CH_3$, $-C(O)-O-CH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, o ciclopropilo.

[0037] En algunas modalidades de los compuestos de la Fórmula I, R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; y R^6 es -H. En algunas modalidades, R^2 y R^4 son -H; R^1 es -O-CH_3; R^3 es -F; R^6 es -H; y R^5 es -H, -Cl, -CN, -C≡CH, -O-CH_3, o fenilo.

[0038] En una modalidad de los compuestos de las Fórmulas I y I', el compuesto se selecciona del grupo que consiste de:

[5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1497**),

(6-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1498**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1499**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1500**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1501**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1502**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1403**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1504**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1505**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1506**),

(6-Cloro-piridin-3-ilmetil)-[6-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1508**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1509**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1510**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1513**),

(6-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1515**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1516**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1520**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1521**),

(6-Cloro-piridin-3-ilmetil)-[4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1523**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1524**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1525**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1528**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1529**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1531**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1533**),

(6-Cloro-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1535**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1536**),

[6-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1537**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1540**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-cloro-piridin-3-ilmetil)-amina (**P-1542**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1543**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1544**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1547**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1548**),

(6-Cloro-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1550**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1551**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1555**),

(6-Cloro-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1557**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1558**),

[3-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1559**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1563**),

(6-Cloro-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1565**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1566**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1567**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1570**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1579**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1581**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1582**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1584**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1586**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1587**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1588**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1590**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-cloro-piridin-3-ilmetil)-amina (**P-1592**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1593**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1594**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1597**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1598**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1599**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1600**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1602**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1603**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina (**P-1607**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1608**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1611**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1612**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1613**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1623**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1625**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1626**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1627**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1630**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1632**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1633**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1634**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1638**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1640**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1641**),

(4-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1642**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1646**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1648**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1649**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1650**),

3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1654**),

3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1655**),

3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1656**),

3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1657**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1661**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1663**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1664**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1665**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1670**),

N-(3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1672**),

N-(3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1673**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1677**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1680**),

N-(3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1681**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1685**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1687**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1688**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1689**),

metiléster del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1693**),

metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1694**),

metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1696**),

metilamida del ácido 3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1697**),

metilamida del ácido 3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1698**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1703**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1704**),

(6-Cloro-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1706**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1707**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1711**),

(6-Cloro-piridin-3-ilmetil)-[5-(4-etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1713**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1714**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1715**),

3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1720**),

3-{6-[(5-Fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1721**),

3-{6-[(4-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1722**),

3-{6-[(5-Fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1726**),

(6-Bromo-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2002**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2003**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina (**P-2004**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2040**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2041**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2042**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2062**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2063**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2064**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2070**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2073**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2078**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2088**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2152**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2153**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**),

[5-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2170**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(4-fenil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2171**),

5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**
6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y
cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0039] En algunas modalidades de los compuestos de las Fórmulas I y I', R^7 es diferente a hidrógeno. Todas las otras variables son como se define en este documento.

[0040] En un grupo de modalidades de los compuestos de las Fórmulas I y I', R^6 y R^7 no son simultáneamente H. Todas las otras variables son como se define en este documento.

[0041] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^7 es halógeno, R^6 es diferente a H, halógeno, heteroarilo, CN o alquilo inferior. En ciertos casos, cuando R^7 es Cl, R^6 es diferente a H, Cl, pirazolilo, CN o CH_3. Todas las otras variables son como se define en este documento.

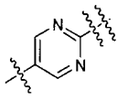
[0042] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^7 es halógeno, R^6 es diferente a alquilo inferior halo sustituido. En ciertos casos, cuando R^7 es Cl, R^6 es diferente a CF_3. Todas las otras variables son como se define en este documento.

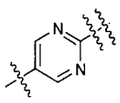
[0043] En un grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^7 es halógeno, R^2 es diferente a alquilo inferior sustituido con halógeno o alcoxi inferior. En ciertos casos, cuando R^7 es Cl, R^2 es diferente a CF_3 o $-OCH_3$. Todas las otras variables son como se define en este documento.

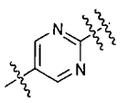
[0044] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^7 es halógeno, R^6 es diferente a halógeno, alcoxi inferior, hidrógeno o CN. En ciertos casos, cuando R^7 es -F, R^6 es diferente a Cl, OCH_3, hidrógeno o CN. En otros casos, cuando R^7 es -F, R^3 es diferente a F. Todas las otras variables son como se define en este documento.

[0045] En un grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^7 es hidrógeno, R^6 es diferente a halógeno, hidrógeno, alquilo inferior, CN o alcoxi inferior. En ciertos casos, cuando R^7 es hidrógeno, R^6 es diferente a H, Cl, F, CH_3, CN, $-OCH_3$. Todas las otras variables son como se define en este documento.

[0046] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando R^9 es halógeno, R^6 es diferente a H o halógeno. En ciertos casos, cuando R^9 es Cl, R^6 es diferente a H o Cl. Todas las otras variables son como se define en este documento.

[0047] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando Ar es  , R^6 es diferente a hidrógeno. Todas las otras variables son como se define en este documento.

[0048] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando Ar es  , R^1, R^2, R^3 y R^4 no son simultáneamente hidrógeno. Todas las otras variables son como se define en este documento.

[0049] En otro grupo de modalidades de los compuestos de las Fórmulas I y I', cuando Ar es  , R^2 es diferente a alquilo inferior halo sustituido, por ejemplo, en una modalidad, R^2 es diferente a CF_3. Todas las otras variables son como se define en este documento.

[0050] Los compuestos excluidos de la Fórmula I' y Fórmula I se listan en la Tabla 1 a continuación.

Tabla 1

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0174)**,

[6-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0176)**,

{6-Cloro-5-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0179)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0186)**,

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0187)**,

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0188)**,

3-{2-Cloro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0232)**,

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0233)**,

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0234)**,

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **(P-0378)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **(P-0379)**,

(5-Fluoro-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0414)**,

3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0415)**,

3-[6-(4-Cloro-bencilamino)-2-fluoro-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0432)**,

Piridin-3-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0094)**,

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0215)**,

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0219)**,

(5-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0222)**,

(5-Fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0230)**,

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0273)**,

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0282)**,

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0284)**,

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0285)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina **(P-0286)**,

3-{6-[(2-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-0287)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **(P-0324)**,

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **(P-0331)**,

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0332)**,

(2-Morfolin-4-il-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0347)**,

(2,6-Dimetoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0370)**,

(6-Ciclopentiloxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0374)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina **(P-0376)**,

(5-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0400)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[6-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina **(P-0409)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0181)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0182)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-3-ilmetil-amina **(P-0164)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0173)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-3-ilmetil-amina **(P-0422)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0429)**,

2,2-Dimetil-N-(3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-il)-propionamida **(P-0384)**,

Metil-(3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-il)-amina **(P-0385)**,

Dimetil-(3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-il)-amina **(P-0399)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-4-ilmetil)-amina **(P-0200)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-3-ilmetil-amina **(P-0236)**,

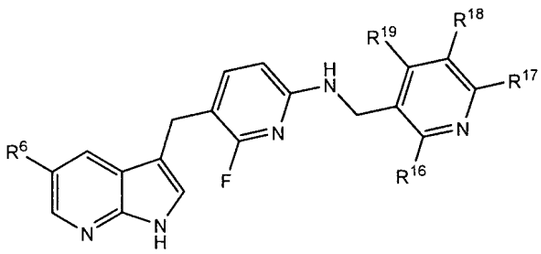
[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina **(P-0241)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0242)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina **(P-0247)**, y

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina (**P-0207**).

[0051] En un segundo aspecto, la presente invención proporciona compuestos que tienen la Fórmula II':



Fórmula II'

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

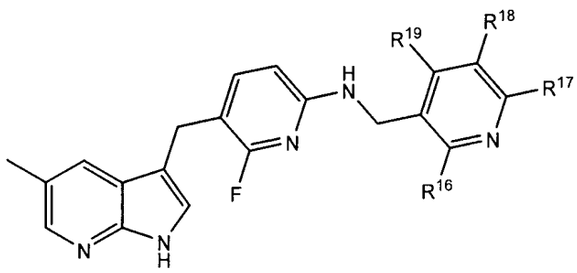
en donde:

R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente del grupo que consiste de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H;

R^{20} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo; R^{21} es alquilo inferior; R^{22} es alquilo inferior; y R^{23} es alquilo inferior.

[0052]] En algunas modalidades de los compuestos de la Fórmula II', R^6 se selecciona del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. En ciertos casos, R^6 es F, Cl, Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} o -N(H)-$S(O)_2$-R^{15}. En otros casos, R^6 es metilo, etilo, propilo, butilo, pentilo o hexilo. Todas las otras variables son como se define en este documento.

[0053] En algunas modalidades, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula II:



Fórmula II

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

R^{16}, R^{17}, R^{18} y R^{19} se seleccionan independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, y -N(H)-S(O)$_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H;

R^{20} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{21} es alquilo inferior;

R^{22} es alquilo inferior; y

R^{23} es alquilo inferior.

[0054] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor , alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, y -N(H)-S(O)$_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean –H. En algunas modalidades, R^{17} y R^{19} son H, halógeno o alquilo inferior. Todas las otras variables son como se define en este documento.

[0055] En otras modalidades de los compuestos de las Fórmulas II y II', R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H. Todas las otras variables son como se define en este documento.

[0056] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16}, R^{17}, y R^{18} son H y R^{19} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es alquilo inferior sustituido con flúor o -O-R^{20}. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es -CF_3 o -O-CH_3. Todas las otras variables son como se define en este documento.

[0057] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, o -O-R^{20}. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, o -O-CH_3. Todas las otras variables son como se define en este documento.

[0058] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16}, R^{18}, y R^{19} son H y R^{17} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R^{17} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R17 es -Cl, alquilo inferior sustituido con flúor, cicloalquilamino, o -O-R^{20}. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R^{17} es -Cl, $-CF_3$, -O-CH_3, o morfolin-4-ilo. Todas las otras variables son como se define en este documento.

[0059] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, $-CF_3$, morfolin-4-ilo, -O-CH_3, -O-CH_2CH_3, -O-$CH(CH_3)_2$, -O-CH_2CF_3, -O-ciclopentilo, -O-ciclohexilo, o -N(H)-CH_3. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, $-CF_3$, o -O-CH_3. Todas las otras variables son como se define en este documento.

[0060] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, o -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, CF_3, -O-CH_3, o -$N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0061] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F,

-Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -CF_3 o -O-CH_3. Todas las otras variables son como se define en este documento.

[0062] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F o -O-CH_3. Todas las otras variables son como se define en este documento.

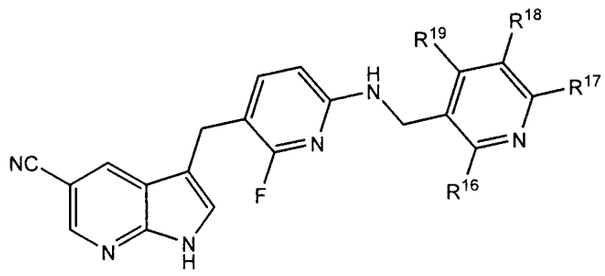
[0063] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. Todas las otras variables son como se define en este documento.

[0064] En algunas modalidades de los compuestos de la Fórmula II, R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente – F, -Cl, o -O-CH_3. Todas las otras variables son como se define en este documento.

[0065] En algunas modalidades de los compuestos de las Fórmulas II y II', R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, CF_3,

-O-CH_3, o -$N(CH_3)_2$. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -CF_3, -O-CH_3, o -$N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0066] En algunas modalidades, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula IIa:



Fórmula IIa

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

R^{16}, R^{17}, R^{18} y R^{19} se seleccionan independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H;

R^{20} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{21} es alquilo inferior;

R^{22} es alquilo inferior; y

R^{23} es alquilo inferior.

[0067] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16}, R^{17}, R^{18} y R^{19} son cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor , alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean –H. En algunas modalidades, R^{17} y R^{19} son H, halógeno o alquilo inferior. Todas las otras variables son como se define en este documento.

[0068] En otras modalidades de los compuestos de la Fórmula IIa, R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada unó independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H. Todas las otras variables son como se define en este documento.

[0069] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16}, R^{17}, y R^{18} son H y R^{19} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con

metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es alquilo inferior sustituido con flúor o -O-R^{20}. En algunas modalidades R^{16}, R^{17}, y R^{18} son H y R^{19} es $-CF_3$ o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0070] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, o -O-R^{20}. En algunas modalidades R^{16}, R^{17}, y R^{19} son H y R^{18} es -F, -Cl, o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0071] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16}, R^{18}, y R^{19} son H y R^{17} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R^{17} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R^{17} es -Cl, alquilo inferior sustituido con flúor, cicloalquilamino, o -O-R^{20}. En algunas modalidades R^{16}, R^{18}, y R^{19} son H y R^{17} es -Cl, $-CF_3$, $-O-CH_3$, o morfolin-4-ilo. Todas las otras variables son como se define en este documento.

[0072] En algunas modalidades de los compuestos de la Fórmula IIa, R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -$N(R^{22})_2$. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, $-CF_3$, morfolin-4-ilo, $-O-CH_3$, $-O-CH_2CH_3$, $-O-CH(CH_3)_2$, $-O-CH_2CF_3$, -O-ciclopentilo, -O-ciclohexilo, o $-N(H)-CH_3$. En algunas modalidades R^{17}, R^{18}, y R^{19} son H y R^{16} es -F, $-CF_3$, o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0073] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -N(H)-R^{22}, -$N(R^{22})_2$, o -N(H)-$S(O)_2$-R^{23}. En algunas modalidades R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o

$-N(R^{22})_2$. En algunas modalidades R^{16} y R^{17} son H; y R^{18} y R^{19} son independientemente -F, -Cl, CF_3, $-O-CH_3$, o $-N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0074]] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, $-O-R^{20}$, $-S(O)_2-R^{21}$, $-N(H)-R^{22}$, $-N(R^{22})_2$, o $-N(H)-S(O)_2-R^{23}$. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-O-R^{20}$, $-N(H)-R^{22}$, o $-N(R^{22})_2$. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente -F, -Cl, CF_3, $-O-CH_3$, o $-N(CH_3)_2$. En algunas modalidades R^{16} y R^{18} son H; y R^{17} y R^{19} son independientemente $-CF_3$ o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0075] En algunas modalidades de los compuestos de la Fórmula IIa, R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, $-O-R^{20}$, $-S(O)_2-R^{21}$, $-N(H)-R^{22}$, $-N(R^{22})_2$, o $-N(H)-S(O)_2-R^{23}$. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-O-R^{20}$, $-N(H)-R^{22}$, o $-N(R^{22})_2$. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F, -Cl, CF_3, $-O-CH_3$, o $-N(CH_3)_2$. En algunas modalidades R^{16} y R^{19} son H; y R^{17} y R^{18} son independientemente -F o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0076] En algunas modalidades de los compuestos de la Fórmula IIa, R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, $-O-R^{20}$, $-S(O)_2-R^{21}$, $-N(H)-R^{22}$, $-N(R^{22})_2$, o $-N(H)-S(O)_2-R^{23}$. En algunas modalidades R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-O-R^{20}$, $-N(H)-R^{22}$, o $-N(R^{22})_2$. En algunas modalidades R^{17} y R^{18} son H; y R^{16} y R^{19} son independientemente -F, -Cl, CF_3, $-O-CH_3$, o $-N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0077] En algunas modalidades de los compuestos de la Fórmula IIa, R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, $-O-R^{20}$, $-S(O)_2-R^{21}$, $-N(H)-R^{22}$, $-N(R^{22})_2$, o $-N(H)-S(O)_2-R^{23}$. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-O-R^{20}$, $-N(H)-R^{22}$, o $-N(R^{22})_2$. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente -F, -Cl, CF_3, $-O-CH_3$, o $-N(CH_3)_2$. En algunas modalidades R^{17} y R^{19} son H; y R^{16} y R^{18} son independientemente – F, -Cl, o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0078] En algunas modalidades de los compuestos de la Fórmula IIa, R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -N(H)-R^{22}, -N(R^{22})$_2$, o -N(H)-S(O)$_2$-R^{23}. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{20}, -N(H)-R^{22}, o -N(R^{22})$_2$. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{18} y R^{19} son H; y R^{16} y R^{17} son independientemente -CF_3, -O-CH_3, o -N(CH_3)$_2$. Todas las otras variables son como se define en este documento.

[0079] En una modalidad de los compuestos de las Fórmulas II y II' y IIa, el compuesto se selecciona del grupo que consiste de:

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2027**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),
(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2047**),
(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),
(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),
(4-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2050**),
(2-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2051**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2052**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina (**P-2058**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2062**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-4-ilmetil)-amina (**P-2065**),
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2067**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2071**),

(2,5-Dimetoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2086**),

(3,5-Dimetoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2087**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2088**),

(3-Bromo-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2089**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-morfolin-4-il-piridin-3-ilmetil)-amina (**P-2090**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-morfolin-4-il-piridin-3-ilmetil)-amina (**P-2091**),

(3-Cloro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2092**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-2-ilmetil)-amina (**P-2093**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-fluoro-piridin-4-ilmetil)-amina (**P-2094**),

(5-{[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-metil-amina (**P-2095**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina (**P-2096**),

(2,6-Dimetoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2097**),

(5-Fluoro-2-metanosulfonil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2098**),

(5-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2099**),

(5-Bromo-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2100**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-metil-piridin-4-ilmetil)-amina (**P-2101**),

(3-Cloro-5-fluoro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2102**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-3-ilmetil)-amina (**P-2103**),

(3,5-Dimetil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2104**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metoxi-piridin-3-ilmetil)-amina (**P-2105**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-pirimidin-5-ilmetil)-amina (**P-2106**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metilamino-piridin-3-ilmetil)-amina (**P-2107**),

(3,5-Bis-trifluorometil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2108**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-metoxi-piridin-3-ilmetil)-amina (**P-2109**),

(2-Etoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2110**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-isopropoxi-piridin-3-ilmetil)-amina (**P-2111**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-metil-piridin-2-ilmetil)-amina (**P-2112**),

(2-Ciclopentiloxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2113**),

(2-Ciclohexiloxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2114**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-piridin-3-ilmetil)-amina (**P-2115**),

(2-Cloro-5-fluoro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2116**),

4-{[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-carbonitrilo (**P-2117**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-4-ilmetil)-amina (**P-2118**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-piridin-4-ilmetil)-amina (**P-2119**),

(2-Cloro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2120**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-morfolin-4-il-piridin-4-ilmetil)-amina (**P-2121**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-pirrolidin-1-il-piridin-4-ilmetil)-amina (**P-2122**),

(5-Cloro-2-fluoro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2123**),

(4-Cloro-2-metanosulfonil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2124**),

(2-Dimetilamino-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2125**),

(2-Etil-pirimidin-5-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2126**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-propil-pirimidin-5-ilmetil)-amina (**P-2127**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-isopropil-pirimidin-5-ilmetil)-amina (**P-2128**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2-metoxi-etil)-pirimidin-5-ilmetil]-amina (**P-2129**),

(2-Butil-pirimidin-5-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2130**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metil-piridin-2-ilmetil)-amina (**P-2131**),

(3-Fluoro-5-metil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2132**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-metoxi-5-trifluorometil-bencil)-amina (**P-2133**),

(3-Fluoro-5-metoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2134**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3,4,5-trimetoxi-bencil)-amina (**P-2150**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2151**),

5-Fluoro-3-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-1-metil-1H-piridin-2-ona (**P-2156**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-6-trifluorometil-piridin-3-ilmetil)-amina (**P-2166**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-dimetilamino-6-trifluorometil-piridin-3-ilmetil)-amina (**P-2167**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-4-trifluorometil-piridin-3-ilmetil)-amina (**P-2186**),

(2-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2198**),

(4-fluoro-3-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2199**),

(3-fluoro-5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2202**),

5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**

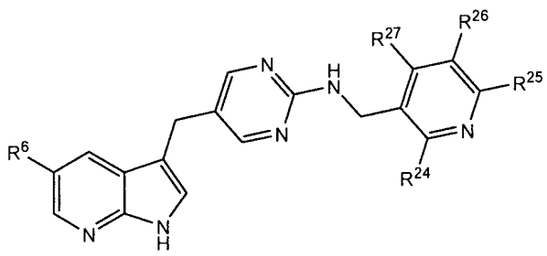
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**

6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**

6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0080] En un tercer aspecto, la invención proporciona compuestos que tienen la Fórmula III':



Fórmula III'

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

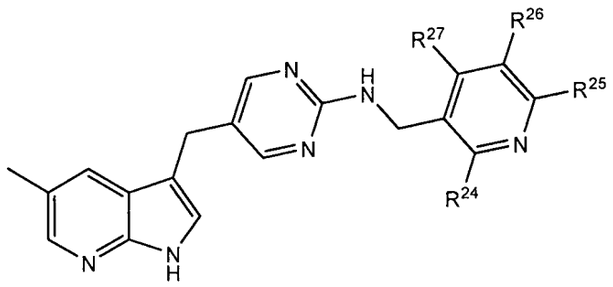
en donde:

R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente del grupo que consiste de -H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, alcoxi inferior, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -$S(O)_2$-N(H)-R^{30}, -N(H)-R^{30}, -$N(R^{30})_2$, y -N(H)-$S(O)_2$-R^{31}, siempre y cuando al menos dos de R^{24}, R^{25}, R^{26} y R^{27}

sean -H; R^{28} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior, o cicloalquilo; R^{29} es alquilo inferior; R^{30} es alquilo inferior; y R^{31} es alquilo inferior.

[0081] En algunas modalidades de los compuestos de la Fórmula III', R^6 se selecciona del grupo que consiste de halógeno, alquilo inferior, alcoxi inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. En otras modalidades de los compuestos de la Fórmula III', R^6 es F, Cl, Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} o -N(H)-$S(O)_2$-R^{15}. En algunas modalidades, R^6 es metilo, etilo, propilo, butilo, pentilo o hexilo. Todas las otras variables son como se define en este documento.

[0082] En algunas modalidades, se proporcionan compuestos que tienen la estructura de acuerdo con la siguiente Fórmula III:



Fórmula III

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

R^{24}, R^{25}, R^{26} y R^{27} se seleccionan independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -$S(O)_2$-N(H)-R^{30}, -N(H)-R^{30}, -N(R^{30})$_2$, y -N(H)-$S(O)_2$-R^{31}, siempre y cuando al menos dos de R^{24}, R^{25}, R^{26} y R^{27} sean -H;

R^{28} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{29} es alquilo inferior;

R^{30} es alquilo inferior; y

R^{31} es alquilo inferior.

[0083] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alquilo inferior sustituido con metoxi,

cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}, siempre y cuando al menos dos de R^{24}, R^{25}, R^{26} y R^{27} sean –H. En algunas modalidades, R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi. Todas las otras variables son como se define en este documento.

[0084] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24}, R^{25}, y R^{26} son H y R^{27} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24}, R^{25}, y R^{26} son H y R^{27} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24}, R^{25}, y R^{26} son H y R^{27} es alquilo inferior sustituido con flúor o -O-R^{28}. En algunas modalidades R^{24}, R^{25}, y R^{26} son H y R^{27} es $-CF_3$ o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0085] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24}, R^{25}, y R^{27} son H y R^{26} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24}, R^{25}, y R^{27} son H y R^{26} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24}, R^{25}, y R^{27} son H y R^{26} es -F, -Cl, o -O-R^{28}. En algunas modalidades R^{24}, R^{25}, y R^{27} son H y R^{26} es -F, -Cl, o $-O-CH_3$. Todas las otras variables son como se define en este documento.

[0086] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24}, R^{26}, y R^{27} son H y R^{25} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24}, R^{26}, y R^{27} son H y R^{25} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24}, R^{26}, y R^{27} son H y R^{25} es -Cl, alquilo inferior sustituido con flúor, cicloalquilamino, o -O-R^{28}. En algunas modalidades R^{24}, R^{26}, y R^{27} son H y R^{25} es -Cl, $-CF_3$, $-O-CH_3$, o 4-metil-piperazin-1-ilo. Todas las otras variables son como se define en este documento.

[0087] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{25}, R^{26}, y R^{27} son H y R^{24} es -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{25}, R^{26}, y R^{27} son H y R^{24} es -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{25}, R^{26}, y R^{27} son H y R^{24} es -F, $-CF_3$, morfolin-4-ilo, $-O-CH_3$, $-O-CH_2CH_3$, $-O-CH(CH_3)_2$, $-O-CH_2CF_3$, -O-ciclopentilo, -O-ciclohexilo, o -N(H)-CH_3. En algunas modalidades R^{25}, R^{26}, y R^{27} son H y R^{24} es

-F, -CF_3; -O-CH_3, -O-CH_2CH_3, o -O-ciclopentilo. Todas las otras variables son como se define en este documento.

[0088] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24} y R^{25} son H; y R^{26} y R^{27} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24} y R^{25} son H; y R^{26} y R^{27} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24} y R^{25} son H; y R^{26} y R^{27} son independientemente -F, -Cl, CF_3, -O-CH_3, o -$N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0089] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24} y R^{26} son H; y R^{25} y R^{27} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24} y R^{26} son H; y R^{25} y R^{27} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24} y R^{26} son H; y R^{25} y R^{27} son independientemente -F, -Cl, CF_3, -O-CH_3, o -$N(CH_3)_2$. En algunas modalidades R^{24} y R^{26} son H; y R^{25} y R^{27} son independientemente $-CF_3$ o -O-CH_3. Todas las otras variables son como se define en este documento.

[0090] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{24} y R^{27} son H; y R^{25} y R^{26} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{24} y R^{27} son H; y R^{25} y R^{26} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{24} y R^{27} son H; y R^{25} y R^{26} son independientemente -F, -Cl, CF_3, -O-CH_3, o -$N(CH_3)_2$. En algunas modalidades R^{24} y R^{27} son H; y R^{25} y R^{26} son independientemente -F o -O-CH_3. Todas las otras variables son como se define en este documento.

[0091] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{25} y R^{26} son H; y R^{24} y R^{27} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -$S(O)_2$-R^{29}, -N(H)-R^{30}, -$N(R^{30})_2$, o -N(H)-$S(O)_2$-R^{31}. En algunas modalidades R^{25} y R^{26} son H; y R^{24} y R^{27} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -$N(R^{30})_2$. En algunas modalidades R^{25} y R^{26} son H; y R^{24} y R^{27} son independientemente -F, -Cl, CF_3, -O-CH_3, o -$N(CH_3)_2$. Todas las otras variables son como se define en este documento.

[0092] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{25} y R^{27} son H; y R^{24} y R^{26} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, o -N(H)-S(O)$_2$-R^{31}. En algunas modalidades R^{25} y R^{27} son H; y R^{24} y R^{26} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -N(R^{30})$_2$. En algunas modalidades R^{25} y R^{27} son H; y R^{24} y R^{26} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{25} y R^{27} son H; y R^{24} y R^{26} son independientemente -F o -O-CH_3. Todas las otras variables son como se define en este documento.

[0093] En algunas modalidades de los compuestos de las Fórmulas III y III', R^{26} y R^{27} son H; y R^{24} y R^{25} son independientemente -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -N(H)-R^{30}, -N(R^{30})$_2$, o -N(H)-S(O)$_2$-R^{31}. En algunas modalidades R^{26} y R^{27} son H; y R^{24} y R^{25} son independientemente -F, -Cl, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, -O-R^{28}, -N(H)-R^{30}, o -N(R^{30})$_2$. En algunas modalidades R^{26} y R^{27} son H; y R^{24} y R^{25} son independientemente -F, -Cl, CF_3, -O-CH_3, o -N(CH_3)$_2$. En algunas modalidades R^{26} y R^{27} son H; y R^{24} y R^{25} son independientemente -CF_3, -O-CH_3, o -N(CH_3)$_2$. Todas las otras variables son como se define en este documento.

[0094] En una modalidad de los compuestos de las Fórmulas III y III', el compuesto se selecciona del grupo que consiste de:

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1569**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1570**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

(2-Metoxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2069**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2072**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2073**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-2-ilmetil-amina (**P-2076**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-3-ilmetil-amina (**P-2077**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2078**),

(6-Metil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2079**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2080**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina (**P-2081**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2082**),

(5-Etil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2083**),

(3-Metil-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2084**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-morfolin-4-il-piridin-4-ilmetil)-amina (**P-2085**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-4-ilmetil-amina (**P-2138**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2139**),

[6-(4-Metil-piperazin-1-il)-piridin-3-ilmetil]-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2140**),

(2-Metil-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2141**),

(2-Etoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2142**),

(2-Ciclopentiloxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2148**),

(2-Ciclopentiloxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2149**), y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0095] En un cuarto aspecto, se proporcionan compuestos en donde el compuesto se selecciona del grupo que consiste de:

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-1496**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1507**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1511**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1512**),

(5-Fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1514**),

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1517**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1518**),

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1519**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1522**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1526**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1527**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1530**),

(6-Metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1532**),

(5-Fluoro-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1534**),

[6-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1538**),

(2-Metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1539**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1541**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1545**),

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1546**),

(5-Fluoro-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1549**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1552**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1553**),

(6-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1554**),

(5-Fluoro-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1556**),

[3-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1560**),

(2-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1561**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1562**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1564**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1568**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1580**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1583**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1585**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1589**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1591**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1595**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1596**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1601**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1604**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1605**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1606**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1609**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1614**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1622**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1624**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1628**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1629**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1631**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1635**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1636**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1637**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1639**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1643**),

(6-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1644**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1645**),

(5-Fluoro-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1647**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1651**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1652**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1653**),

3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1658**),

3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1659**),

3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1660**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1662**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1666**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1667**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1668**),

N-(3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1671**),

N-(3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1674**),

N-(3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1675**),

N-(3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1676**),

N-(3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1678**),

N-(3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1682**),

N-(3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1683**),

N-(3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1684**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1686**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1690**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1691**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1692**),

metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1695**),

metilamida del ácido 3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1699**),

metilamida del ácido 3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1700**),

metilamida del ácido 3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1701**),

ter-butiléster del ácido 4-[4-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-pirazol-1-il]-piperidin-1-carboxílico (**P-1702**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(5-fluoro-piridin-3-ilmetil)-amina (**P-1705**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(6-metoxi-piridin-3-ilmetil)-amina (**P-1708**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1709**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(2-metoxi-piridin-3-ilmetil)-amina (**P-1710**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1712**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1716**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1717**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1718**),

3-{6-[(5-Fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1719**),

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1723**),

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1724**),

3-{6-[(2-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1725**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1727**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1728**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1729**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1730**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1731**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1732**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1733**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1734**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2001**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina (**P-2005**),

(3-Cloro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina (**P-2006**),

(3-Cloro-4-metil-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2007**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3,4-difluoro-bencil)-amina (**P-2008**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-5-trifluorometil-bencil)-amina (**P-2009**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometoxi-bencil)-amina (**P-2010**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-4-trifluorometil-bencil)-amina (**P-2011**),

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-metil-amina (**P-2012**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-metil-bencil)-amina (**P-2013**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-4-metil-bencil)-amina (**P-2014**),

[2-(3-Cloro-fenil)-etil]-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2015**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**P-2016**),

[5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2017**),

[5-(4-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2018**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

[2-(2-Cloro-fenil)-etil]-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2020**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[2-(4-fluoro-fenil)-etil]-amina (**P-2021**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[2-(6-metil-piridin-2-il)-etil]-amina (**P-2022**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2023**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2024**),

Butil-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2026**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2028**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

(2-Fluoro-bencil)-[5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2033**),

(2-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2034**),

(2-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2035**),

(2-Cloro-bencil)-[5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2036**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(1-tiazol-2-il-etil)-amina (**P-2039**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2043**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2044**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2045**),

[1-(4-Fluoro-fenil)-propil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2053**),

[1-(4-Fluoro-fenil)-ciclopropil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2055**),

[(S)-1-(4-Fluoro-fenil)-etil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2056**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-4-ilmetil)-amina (**P-2074**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2075**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2135**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2136**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2143**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2144**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2145**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2146**),

[3-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2147**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2154**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2155**),

3-{[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-ilamino]-metil}-5-fluoro-1-metil-1H-piridin-2-ona (**P-2157**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2158**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2159**),

(6-Metoxi-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2162**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina (**P-2163**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-2164**),

5-Fluoro-N-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-2-metoxi-nicotinamida (**P-2168**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2172**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2176**),

N-[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-C-fenil-metanosulfonamida (**P-2181**), y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0096] En referencia a los compuestos en este documento, a menos que se indique claramente lo contrario, la especificación de un compuesto o grupo de compuestos incluye sales de tal o tales compuestos (incluyendo sales farmacéuticamente aceptables), formulaciones de tal o tales compuestos (incluyendo formulaciones farmacéuticamente aceptables), conjugados de los mismos, derivados de los mismos, formas de los mismos, profármacos de los mismos, y todos los estereoisómeros de los mismos. En referencia a las composiciones, equipos, métodos de uso, etc. de los compuestos como se describe en este documento (es decir, compuestos de la invención), se entenderá (a menos que se indique de otra manera) que un compuesto como se describe en este documento incluye compuestos de las Fórmulas I y I' incluyendo todas las sub-modalidades de los mismos, compuestos de las Fórmulas II, II' y IIa, incluyendo todas las sub-modalidades de los mismos, compuestos de las Fórmulas III y III' incluyendo todas las sub-modalidades de los mismos, y compuestos como se listan en el cuarto aspecto anteriormente.

[0097] En un quinto aspecto, se proporcionan métodos para tratar cualquiera de una enfermedad o padecimiento mediado por proteína cinasas Fms y/o Kit y/o Flt-3 en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos, como se describe en este documento. En ciertas modalidades, el método implica administrar al sujeto una cantidad efectiva de un compuesto, como se describe en este documento, en combinación con una o más terapias diferentes para la enfermedad o padecimiento.

[0098] En un sexto aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por proteína cinasa Fms en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, el método implica administrar al sujeto una cantidad efectiva de un compuesto, como se describe en este documento, en combinación con una o más terapias diferentes para la enfermedad o padecimiento.

[0099] En un séptimo aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por proteína cinasa Kit en un sujeto animal en necesidad de ello, en donde el método implica administrar al sujeto una cantidad efectiva de uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, el método implica administrar al sujeto una cantidad efectiva de un compuesto descrito en este documento, en combinación con una o más terapias diferentes para la enfermedad o padecimiento.

[0100] En un octavo aspecto, un compuesto, como se describe en este documento, tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms. En algunas modalidades, el compuesto es selectivo en relación con otras proteína cinasas, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms, sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0101] En un noveno aspecto, un compuesto, como se describe en este documento, tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Kit. En algunas modalidades, el compuesto es selectivo en relación con otras proteína cinasas, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Kit, sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0102] En un décimo aspecto, un compuesto, como se describe en este documento, es un inhibidor dual de Fms/Kit, es decir, será de potencia aproximadamente igual con respecto a la inhibición de cinasa Fms y cinasa Kit. En algunas modalidades el compuesto tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, en donde la relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. En algunas modalidades, el compuesto es selectivo en relación con proteína cinasas diferentes a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms, sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. En una modalidad, el inhibidor dual de Fms/Kit es un compuesto seleccionado del grupo que consiste de:

(6-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1554**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1562**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2003**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina (**P-2004**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3,4-difluoro-bencil)-amina (**P-2008**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-metil-bencil)-amina (**P-2013**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

(6-Metil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2079**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina (**P-2081**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2082**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metil-piridin-2-ilmetil)-amina (**P-2131**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2146**),

[3-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2147**),

(2-Ciclopentiloxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2148**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2154**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina (**P-2163**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2172**),

(2-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2198**),

(3-fluoro-5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2202**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**

3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**

6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**

6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0103] En un decimoprimer aspecto, un compuesto, como se describe en este documento, es un inhibidor selectivo de Fms, es decir, inhibirá de manera selectiva la cinasa Fms en relación con la cinasa Kit. En algunas modalidades, el compuesto tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y, cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, tendrá un relación de IC_{50} para cinasa Kit, dividida entre la IC_{50} para cinasa Fms, de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. En algunas modalidades, el compuesto también es selectivo en relación con proteína cinasas diferentes a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms, sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, Flt-3, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. En una modalidad, el inhibidor selectivo de Fms es un compuesto seleccionado del grupo que consiste de:

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-1496**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1622**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1669**),

N-(3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1679**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2001**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2028**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2043**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2045**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2052**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2062**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2063**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2064**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2067**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2070**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2071**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2073**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2075**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2078**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2088**),

(2,6-Dimetoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2097**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-3-ilmetil)-amina (**P-2103**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-4-ilmetil)-amina (**P-2118**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2139**),

3-{[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-ilamino]-metil}-5-fluoro-1-metil-1H-piridin-2-ona (**P-2157**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2176**),

3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-2193**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**
6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y
cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0104] En un decimosegundo aspecto, un compuesto, como se describe en este documento, es un inhibidor dual de Fms/Flt-3, es decir, será de potencia aproximadamente igual con respecto a la inhibición de cinasa Fms y cinasa Flt-3. En algunas modalidades el compuesto tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Flt-3, en donde la relación de IC_{50} para cinasa Flt-3 dividida entre la IC_{50} para cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. En algunas modalidades, el compuesto es selectivo en relación con proteína cinasas diferentes a Flt-3, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms, sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. En algunas modalidades, el inhibidor dual de Fms/Flt-3 también inhibe a Kit. En una modalidad, el inhibidor dual de Fms/Flt-3 es un compuesto seleccionado del grupo que consiste de:

(6-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1644**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1646**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1667**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2003**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina (**P-2004**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-5-trifluorometil-bencil)-amina (**P-2009**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

(2-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2034**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2040**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2041**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2044**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2047**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2050**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**
6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y
cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0105] En una modalidad, el inhibidor dual de Fms/Flt-3 es un compuesto seleccionado del grupo que consiste de:

(6-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1644**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1646**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1667**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-5-trifluorometil-bencil)-amina (**P-2009**),

(2-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2034**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2040**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2041**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2044**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2047**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2050**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**
6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**, y
cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

[0106] Además de cualquiera de los aspectos y modalidades referidos en este documento, un compuesto, como se describe en este documento, también inhibe los efectos de una mutación de la cinasa (por ejemplo, mutante de Fms, mutante de Kit, mutante de Flt-3), incluyendo, pero sin limitarse a, una mutación que se relaciona con una condición de enfermedad, tal como un cáncer.

[0107] En un decimotercer aspecto, se proporcionan composiciones que incluyen una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos, como se describe en este documento, y al menos un portador, excipiente, y/o diluyente farmacéuticamente aceptable, incluyendo combinaciones de dos cualesquiera o más compuestos, como se describe en este documento. La composición además puede incluir una pluralidad de diferentes compuestos farmacológicamente activos, los cuales pueden incluir una pluralidad de compuestos, como se describe en este documento. En ciertas modalidades, la composición puede incluir uno cualquiera o más compuestos, como se describe en este documento, en conjunto con uno o más compuestos que son terapéuticamente

efectivos para la misma indicación de enfermedad. En un aspecto, la composición incluye uno cualquiera o más compuestos, como se describe en este documento, en conjunto con uno o más compuestos que son terapéuticamente efectivos para la misma indicación de enfermedad, en donde los compuestos tienen un efecto sinérgico sobre la indicación de enfermedad. En una modalidad, la composición incluye uno cualquiera o más compuestos, como se describe en este documento, efectivos para tratar un cáncer y uno o más compuestos diferentes que son efectivos para tratar el mismo cáncer, además en donde los compuestos son sinérgicamente efectivos para tratar el cáncer.

[0108] En un decimocuarto aspecto, se proporcionan métodos para modular la actividad de una proteína cinasa Fms y/o Kit y/o Flt-3, incluyendo cualquier mutación de las mismas, al poner en contacto la proteína cinasa con una cantidad efectiva de uno cualquiera o más compuestos, como se describe en este documento.

[0109] En un decimoquinto aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y/o Kit y/o Flt-3, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y/o Kit, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0110] En un decimosexto aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0111] En un decimoséptimo aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Kit, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Kit, incluyendo

cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0112] En un decimoctavo aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Flt-3, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Flt-3, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0113] En un decimonoveno aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Flt-3, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Flt-3, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0114] En un vigésimo aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Kit, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento. En una modalidad, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Kit, incluyendo cualquier mutación de las mismas, en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con una o más terapias adecuadas diferentes para tratar la enfermedad.

[0115] En un vigesimoprimer aspecto, la invención proporciona un método para tratar un cáncer en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con

una o más terapias o procedimientos médicos diferentes, efectivos para tratar al cáncer. Otras terapias o procedimientos médicos incluyen terapia anti cáncer adecuada (por ejemplo, terapia farmacológica, terapia con vacunas, terapia génica, terapia fotodinámica) o procedimiento médico (por ejemplo, cirugía, tratamiento con radiación, calefacción hipertérmica, trasplante de médula ósea o células madre). En una modalidad, la o las terapias anti cáncer o procedimientos médicos adecuados se seleccionan del tratamiento con un agente quimioterapéutico (por ejemplo, fármaco quimioterapéutico), tratamiento con radiación (por ejemplo, rayos x , rayos γ, o haz de electrones, protones, neutrones, o partículas α), calefacción hipertérmica (por ejemplo, microondas, ultrasonido, por radiofrecuencia), Terapia con vacunas (por ejemplo, vacuna de carcinoma hepatocelular gen AFP, vacuna de vector adenoviral AFP, AG-858, vacuna alogénica de cáncer de mama con secreción de GM-CSF, vacunas peptídicas de células dendríticas), terapia génica (por ejemplo, vector Ad5CMV-p53, adenovector que codifica MDA7, adenovirus 5-factor de necrosis tumoral alfa), terapia fotodinámica (por ejemplo, ácido aminolevulínico, texaferina de lutecio), cirugía, o trasplante de médula ósea y células madre.

[0116] En un vigesimosegundo aspecto, la invención proporciona un método para tratar un cáncer en un sujeto en necesidad de ello, al administrar al sujeto una cantidad efectiva de una composición que incluye uno cualquiera o más compuestos, como se describe en este documento, en combinación con uno o más agentes quimioterapéuticos adecuados. En una modalidad, el o los agentes quimioterapéuticos adecuados se seleccionan de un agente alquilante, incluyendo, pero sin limitarse a, adozelesina, altretamina, bendamustina, bizelesina, busulfano, carboplatina, carbocuona, carmofur, carmustina, clorambucil, cisplatina, ciclofosfamida, dacarbazina, estramustina, etoglucid, fotemustina, hepsulfamo, ifosfamida, improsulfano, irofulveno, lomustina, manosulfano, mecloretamina, melfalano, mitobronitol, nedaplatina, nimustina, oxaliplatina, piposulfano, prednimustina, procarbazina, ranimustina, satraplatina, semustina, estreptozocina, temozolomida, tiotepa, treosulfano, triazicuona, trietilenmelamina, tetranitrato de triplatina, trofosfamida, y uramustina; un antibiótico, incluyendo, pero sin limitarse a, aclarubicina, amrubicina, bleomicina, dactinomicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina, idarubicina, menogaril, mitomicina, neocarzinostatina, pentostatina, pirarubicina, plicamicina, valrubicina, y zorubicina; un antimetabolito, incluyendo, pero sin limitarse a, aminopterina, azacitidina, azatioprina, capecitabina, cladribina, clofarabina, citarabina, decitabina, floxuridina, fludarabina, 5-fluorouracilo, gemcitabina, hidroxiurea, mercaptopurina, metotrexato, nelarabina, pemetrexed, raltitrexed, tegafur-uracilo, tioguanina, trimetoprim, trimetrexato, y vidarabina; una inmunoterapia, incluyendo, pero sin limitarse a, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, 90 Y ibritumomab tiuxetano, ipilimumab, y tremelimumab; una hormona o antagonista de hormonas, incluyendo, pero sin limitarse a, anastrozol, andrógenos, buserelina, dietilestilbestrol, exemestano, flutamida, fulvestrant, goserelina, idoxifeno, letrozol, leuprólido,

magestrol, raloxifeno, tamoxifeno, y toremifeno; un taxano, incluyendo, pero sin limitarse a, DJ-927, docetaxel, TPI 287, larotaxel, ortataxel, paclitaxel, DHA-paclitaxel, y tesetaxel; un retinoide, incluyendo, pero sin limitarse a, alitretinoina, bexaroteno, fenretinida, isotretinoina, y tretinoina; un alcaloide, incluyendo, pero sin limitarse a, demecolcina, homoharringtonina, vinblastina, vincristina, vindesina, vinflunina, y vinorelbina; un agente antiangiogénico, incluyendo, pero sin limitarse a, AE-941 (GW786034, Neovastat), ABT-510, 2-metoxiestradiol, lenalidomida, y talidomida; un inhibidor de topoisomerasa, incluyendo, pero sin limitarse a, amsacrina, belotecano, edotecarina, etopósido, fosfato de etopósido, exatecano, irinotecano (también metabolito activo SN-38 (7-etil-10-hidroxi-camptotecina)), lucantona, mitoxantrona, pixantrona, rubitecano, tenipósido, topotecano, y 9-aminocamptotecina; un inhibidor de cinasas, incluyendo, pero sin limitarse a, axitinib (AG 013736), dasatinib (BMS 354825), erlotinib, gefitinib, flavopiridol, mesilato de imatinib, lapatinib, difosfato de motesanib (AMG 706), nilotinib (AMN107), seliciclib, sorafenib, malato de sunitinib, AEE-788, BMS-599626, UCN-01 (7-hidroxistaurosporina), y vatalanib; un inhibidor orientado de la transducción de señales incluyendo, pero sin limitarse a bortezomib, geldanamicina, y rapamicina; un modificador de respuestas biológicas, incluyendo, pero sin limitarse a, imiquimod, interferón-α, e interleucina-2; y otros quimioterapéuticos, incluyendo, pero sin limitarse a 3-AP (3-amino-2-carboxialdehído tiosemicarbazona), altrasentan, aminoglutetimida, anagrelida, asparaginasa, briostatina-1, cilengitida, elesclomol, mesilato de eribulina (E7389), ixabepilona, lonidamina, masoprocol, mitoguanazona, oblimersen, sulindaco, testolactona, tiazofurina, inhibidores de mTOR (por ejemplo, temsirolimus, everolimus, deforolimus), inhibidores de PI3K (por ejemplo, BEZ235, GDC-0941, XL147, XL765), inhibidores de Cdk4 (por ejemplo, PD-332991), inhibidores de Akt, inhibidores de Hsp90 (por ejemplo, tanespimicina) e inhibidores de farnesiltransferasa (por ejemplo, tipifarnib). Preferentemente, el método para tratar un cáncer implica administrar al sujeto una cantidad efectiva de una composición incluyendo uno cualquiera o más compuestos de las Fórmulas I o I', en combinación con un agente quimioterapéutico seleccionado de capecitabina, 5-fluorouracilo, carboplatina, dacarbazina, gefitinib, oxaliplatina, paclitaxel, SN-38, temozolomida, vinblastina, bevacizumab, cetuximab, interferón-α, interleucina-2, o erlotinib.

[0117] En un vigesimotercer aspecto, la invención proporciona un método para tratar una enfermedad o padecimiento en un sujeto en necesidad de ello, al administrar al sujeto una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos, como se describe en este documento, un profármaco de tal compuesto, una sal farmacéuticamente aceptable de tal compuesto o profármaco, o una formulación farmacéuticamente aceptable de tal compuesto o profármaco. El compuesto puede estar solo o puede ser parte de una composición. En una modalidad, la invención proporciona un método para tratar una enfermedad o padecimiento en un sujeto en necesidad de ello, al administrar al sujeto una cantidad terapéuticamente efectiva de uno cualquiera o más compuestos, como se describe en este documento, un profármaco de tal compuesto, una sal farmacéuticamente aceptable de tal

compuesto o profármaco, o una formulación farmacéuticamente aceptable de tal compuesto o profármaco en combinación con una o más terapias diferentes, adecuadas para la enfermedad o padecimiento.

[0118] En un vigesimocuarto aspecto, la invención proporciona equipos que incluyen un compuesto o composición del mismo, como se describe en este documento. En algunas modalidades, el compuesto o composición se empaca, por ejemplo, en un vial, botella, frasco, el cual además puede empacarse, por ejemplo, dentro de una caja, envoltura, o bolsa; el compuesto o composición se aprueba por la Administración de Alimentos y Fármacos de E. U. o entidad reguladora similar para su administración a un mamífero, por ejemplo, un humano; el compuesto o composición se aprueba para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por proteína cinasas Fms y/o Kit; el equipo de la invención incluye instrucciones escritas para su uso y/u otra indicación de que el compuesto o composición son adecuados o están aprobados para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por proteína cinasas Fms y/o Kit; y el compuesto o composición se empaca en forma de dosis unitaria o dosis única, por ejemplo, píldoras, cápsulas, o similares de dosis única.

[0119] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más los compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Kit en un sujeto en necesidad de ello (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad anormal de Kit (por ejemplo, actividad de cinasa). En algunas modalidades los métodos de la invención pueden implicar administrar, al sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por c-kit, una cantidad efectiva de uno o más compuestos como se describe en este documento. En una modalidad, la enfermedad mediada por Kit se selecciona del grupo que consiste de malignidades, incluyendo, pero sin limitarse a, tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas (NSCLC), cáncer testicular, cáncer pancreático, cáncer de mama, carcinoma de células de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, tumores de estroma gastrointestinal (GISTs), angiogénesis tumoral, 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 tumores de mastocitos caninos; enfermedad cardiovascular, incluyendo, pero sin limitarse a, ateroesclerosis, cardiomiopatía, falla cardiaca, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, alergia,

anafilaxia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome intestinal inflamatorio, rechazo de trasplantes, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, enfermedad de reflujo gastroesofágico (GERD), esofagitis, y úlceras del tracto gastrointestinal; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis y retinitis; e indicaciones neurológicas, incluyendo, pero sin limitarse a, migraña.

[0120] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más los compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms en un sujeto en necesidad de ello (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad anormal de Fms (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar, al sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por Fms, una cantidad efectiva de uno o más compuestos como se describe en este documento. En una modalidad, la enfermedad mediada por Fms se selecciona del grupo que consiste de indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, artritis reumatoide, osteoartritis, artritis psoriática, 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 (SLE), púrpura trombocitopénica inmune (ITP), preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, enfermedad pulmonar obstructiva crónica (COPD), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de activación de macrófagos), reticulohistiocitosis multicéntrica, y ateroesclerosis; trastornos metabólicos, incluyendo, pero sin limitarse a, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, obesidad, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero sin limitarse a, osteoporosis, osteodistrofia, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, osteólisis mediada por infección (por ejemplo, osteomielitis), y osteólisis peri-prostética o mediada por restos de desgaste; enfermedades renales y genitourinarias, incluyendo, pero sin limitarse a, endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal; trastornos del sistema nervioso, incluyendo, pero sin limitarse a, trastornos desmielinizantes (por ejemplo, esclerosis múltiple, síndrome de Charcot Marie Tooth), esclerosis lateral amiotrófica (ALS), miastenia grave, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson; dolor, incluyendo, pero sin limitarse a, dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático,

dolor óseo; malignidades, incluyendo, pero sin limitarse a, mieloma múltiple, leucemia mieloide aguda (AML), leucemia mieloide crónica (CML), cáncer de pulmón, cáncer pancreático, cáncer de próstata, cáncer de mama, cáncer ovárico, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes, (por ejemplo, tumor de células gigantes de hueso, tumor de células gigantes de vaina tendinosa (TGCT)), sinovitis villonodular pigmentada (PVNS), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis de tumores a otros tejidos, metástasis óseas osteolíticas, y otras enfermedades mieloproliferativas crónicas tales como mielofibrosis; vasculitis, incluyendo, pero sin limitarse a, enfermedad vascular de la colágena, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fiebre familiar del Mediterráneo, vasculitis de Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; trastornos heredados, incluyendo, pero sin limitarse a, querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo, pero sin limitarse a, infecciones asociadas con virus de inmunodeficiencia humana, virus de hepatitis B, virus de hepatitis C, anaplasmosis granulocítica humana; trastornos de almacenamiento lisosómico, incluyendo, pero sin limitarse a, enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, cirrosis hepática; indicaciones pulmonares, incluyendo, pero sin limitarse a, fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducida por ventilador, inducida por fumar o por toxinas); e indicaciones quirúrgicas, incluyendo, pero sin limitarse a, cirugía de derivación (cardiopulmonar), cirugía vascular, e injertos vasculares.

[0121] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más los compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Kit en un sujeto en necesidad de ello (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento caracterizado por actividad de Fms y actividad de Kit anormales (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar, al sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por Fms y Kit, una cantidad efectiva de uno o más compuestos como se describe en este documento. En una modalidad, el padecimiento mediado por Fms y Kit se selecciona del grupo que consiste de artritis reumatoide, osteoartritis, artritis psoriática, psoriasis, dermatitis, alergia, anafilaxia, asma, rinitis alérgica, espondilitis anquilosante, polimiositis, dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, enfermedad de Sjogren, histiocitosis de células de Langerhans, enfermedad de Still, enfermedad intestinal inflamatoria, colitis ulcerativa, enfermedad de Crohn, lupus eritematoso sistémico, púrpura

trombocitopénica inmune, preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, enfermedad pulmonar obstructiva crónica, enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico, reticulohistiocitosis multicéntrica, hipereosinofilia, y diabetes tipo I con urticaria, diabetes tipo II, insensibilidad a insulina, hiperglucemia, obesidad, y lipólisis, osteoporosis, osteodistrofia, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, osteólisis mediada por infección, y osteólisis peri-prostética o mediada por restos de desgaste, endometriosis, nefritis, necrosis tubular, complicaciones renales asociadas a diabetes, e hipertrofia renal, esclerosis múltiple, síndrome de Charcot Marie Tooth, esclerosis lateral amiotrófica, miastenia grave, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson, dolor agudo, dolor neuropático, dolor inflamatorio, dolor crónico, migraña, mieloma múltiple, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia mieloidé crónica, tumores de mastocitos, tumores de mastocitos caninos, cáncer de pulmón, cáncer testicular, cáncer pancreático, cáncer de próstata, cáncer de mama, cáncer ovárico, carcinoma de células de merkel, carcinomas del tracto genital femenino, carcinoma colorectal, carcinoma in situ, tumores de estroma gastrointestinal, angiogénesis tumoral, astrocitoma, neuroblastoma, sarcoma, osteosarcoma, sarcomas de origen neuroectodérmico, tumor de células gigantes de hueso, tumor de células gigantes de vaina tendinosa, sinovitis villonodular pigmentada, melanoma, glioblastoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, neurofibromatosis (incluyendo neoplasia de células de Schwann asociada con neurofibromatosis), mastocitosis, metástasis de tumores a otros tejidos, metástasis óseas osteolíticas, y otras enfermedades mieloproliferativas crónicas tales como mielofibrosis, enfermedad vascular de la colágena, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fiebre familiar del Mediterráneo, vasculitis de Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu, uveítis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética, querubismo, neurofibromatosis, infecciones asociadas con virus de inmunodeficiencia humana, virus de hepatitis B, virus de hepatitis C, anaplasmosis granulocítica humana, enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick, cirrosis hepática, enfermedad de reflujo gastroesofágico, esofagitis, y úlceras del tracto gastrointestinal, fibrosis pulmonar, lesión pulmonar aguda, cirugía de derivación, cirugía vascular, e injertos vasculares, ateroesclerosis, cardiomiopatía, falla cardiaca, e hipertensión arterial pulmonar.

[0122] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más los compuestos como se describe en este documento, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por Fms y Flt-3 en un sujeto en necesidad de ello (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos), por ejemplo, una enfermedad o padecimiento

caracterizado por actividad de Fms y actividad de Flt-3 anormales (por ejemplo, actividad de cinasa). En algunas modalidades, los métodos de la invención pueden implicar administrar, al sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por Fms y Flt-3, una cantidad efectiva de uno o más compuestos como se describe en este documento. En una modalidad, el padecimiento mediado por Fms y Flt-3 es leucemia mieloide aguda.

[0123] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o padecimiento seleccionado del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteólisis peri-prostética, esclerosis sistémica, trastornos desmielinizantes, esclerosis múltiple, síndrome de Charcot Marie Tooth, esclerosis lateral amiotrófica, enfermedad de Alzheimer, enfermedad de Parkinson, colitis ulcerativa, enfermedad de Crohn, púrpura trombocitopénica inmune, aterosclerosis, lupus eritematoso sistémico, preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de mama metastásico, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer ovárico, gliomas, glioblastomas, neurofibromatosis, metástasis óseas osteolíticas, metástasis de cerebro, tumores de estroma gastrointestinal, y tumores de células gigantes.

[0124] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o padecimiento seleccionado del grupo que consiste de artritis reumatoide, tumores de estroma gastrointestinal, melanoma, y neurofibromatosis, en donde el compuesto es un inhibidor de Kit, es decir, tiene una IC_{50} de menos de 500 nm, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Kit.

[0125] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o padecimiento seleccionado del grupo que consiste de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, enfermedad de Parkinson, artritis reumatoide, osteoartritis, aterosclerosis, lupus

eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, e hipertrofia renal, en donde el compuesto es un inhibidor selectivo de Fms, es decir, tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y, cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, tendrá una relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100; en algunas modalidades, el compuesto también es selectivo en relación con proteína cinasas diferentes a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, Flt-3, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0126] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o padecimiento seleccionado del grupo que consiste de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, y enfermedad de Parkinson, en donde el compuesto es un inhibidor selectivo de Fms, es decir, tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y, cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, tendrá una relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, y en donde el compuesto cruza de manera efectiva la barrera hematoencefálica; en algunas modalidades, el compuesto también es selectivo en relación con una proteína cinasa diferente a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, Flt-3, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0127] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o

padecimiento seleccionado del grupo que consiste de artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, e hipertrofia renal, en donde el compuesto es un inhibidor selectivo de Fms, es decir, tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y, cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, tendrá una relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, y en donde el compuesto no cruza de manera efectiva la barrera hematoencefálica; en algunas modalidades, el compuesto también es selectivo en relación con una proteína cinasa diferente a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable, dividida entre la IC_{50} para cinasa Fms sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, Flt-3, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0128] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de una enfermedad o padecimiento seleccionado del grupo que consiste de cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide, y esclerosis múltiple, en donde el compuesto es un inhibidor dual de Fms/Kit, es decir, tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms, y tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, en donde la relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2; en algunas modalidades, el compuesto también es selectivo en relación con una proteína cinasa diferente a Kit, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable dividida entre la IC_{50} para cinasa Fms sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0129] En aspectos y modalidades que implican el tratamiento de una enfermedad o padecimiento con uno o más de los compuestos descritos en este documento, los métodos de la invención pueden implicar administrar una cantidad efectiva de uno o más compuestos, como se describe en este documento, a un sujeto en necesidad de ello que adolece o está en riesgo de leucemia mieloide aguda, en donde el compuesto es un inhibidor dual de Fms/Flt-3, es decir, tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms, y tendrá una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Flt-3, en donde la relación de IC_{50} para cinasa Flt-3 dividida entre la IC_{50} para cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2; en algunas modalidades, el compuesto también es selectivo en relación con una proteína cinasa diferente a Flt-3, de tal modo que la relación de IC_{50} para otra cinasa valorada de manera comparable dividida entre la IC_{50} para cinasa Fms sea >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100, en donde la otra proteína cinasa incluye, pero no se limita a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR.

[0130] En un vigesimoquinto aspecto, uno o más compuestos o composiciones, como se describe en este documento, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por Kit, seleccionado del grupo que consiste de malignidades, incluyendo, pero sin limitarse a, tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas, cáncer testicular, cáncer pancreático, cáncer de mama, carcinoma de células de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, tumores de estroma gastrointestinal, angiogénesis tumoral, 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 tumores de mastocitos caninos; enfermedad cardiovascular, incluyendo, pero sin limitarse a, ateroesclerosis, cardiomiopatía, falla cardiaca, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, alergia, anafilaxis, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, enfermedad intestinal inflamatoria, rechazo de trasplantes, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, enfermedad de reflujo gastroesofágico, esofagitis y úlceras del tracto gastrointestinal; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis y retinitis; e indicaciones neurológicas, incluyendo, pero sin limitarse a, migraña. La invención además proporciona uno o más compuestos o composiciones, como se describe en este documento, para su uso para tratar una enfermedad o padecimiento mediado por Kit, como se describe en este documento.

[0131] En un vigesimosexto aspecto, uno o más compuestos, como se describe en este documento, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por Fms seleccionado del grupo que consiste de indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, artritis reumatoide, osteoartritis, artritis psoriática, 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 (SLE), púrpura trombocitopénica inmune (ITP), preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, enfermedad pulmonar obstructiva crónica (COPD), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de activación de macrófagos), reticulohistiocitosis multicéntrica, y ateroesclerosis; trastornos metabólicos, incluyendo, pero sin limitarse a, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, obesidad, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero sin limitarse a, osteoporosis, osteodistrofia, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, osteólisis mediada por infección (por ejemplo, osteomielitis), y osteólisis peri-prostética o mediada por restos de desgaste; enfermedades renales y genitourinarias, incluyendo, pero sin limitarse a, endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal; trastornos del sistema nervioso, incluyendo, pero sin limitarse a, trastornos desmielinizantes (por ejemplo, esclerosis múltiple, síndrome de Charcot Marie Tooth), esclerosis lateral amiotrófica (ALS), miastenia grave, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson; dolor, incluyendo, pero sin limitarse a, dolor crónico, dolor agudo, dolor inflamatorio, dolor neuropático, dolor óseo; malignidades, incluyendo, pero sin limitarse a, mieloma múltiple, leucemia mieloide aguda (AML), leucemia mieloide crónica (CML), cáncer de pulmón, cáncer pancreático, cáncer de próstata, cáncer de mama, cáncer ovárico, neuroblastoma, sarcoma, osteosarcoma, tumores de células gigantes, (por ejemplo, tumor de células gigantes de hueso, tumor de células gigantes de vaina tendinosa (TGCT)), sinovitis villonodular pigmentada (PVNS), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis de tumores a otros tejidos, metástasis óseas osteolíticas, y otras enfermedades mieloproliferativas crónicas tales como mielofibrosis; vasculitis, incluyendo, pero sin limitarse a, enfermedad vascular de la colágena, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fiebre familiar del Mediterráneo, vasculitis de Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; trastornos heredados, incluyendo, pero sin limitarse a, querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo,

pero sin limitarse a, infecciones asociadas con virus de inmunodeficiencia humana, virus de hepatitis B, virus de hepatitis C, anaplasmosis granulocítica humana; trastornos de almacenamiento lisosómico, incluyendo, pero sin limitarse a, enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, cirrosis hepática; indicaciones pulmonares, incluyendo, pero sin limitarse a, fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducida por ventilador, inducida por fumar o por toxinas); e indicaciones quirúrgicas, incluyendo, pero sin limitarse a, cirugía de derivación (cardiopulmonar), cirugía vascular, e injertos vasculares. La invención además proporciona uno o más compuestos o composiciones, como se describe en este documento, para su uso para tratar una enfermedad o padecimiento mediado por Fms, como se describe en este documento.

[0132] En un vigesimoséptimo aspecto, uno o más compuestos, como se describe en este documento, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por Fms y mediado por Kit, seleccionado del grupo que consiste de artritis reumatoide, osteoartritis, artritis psoriática, psoriasis, dermatitis, alergia, anafilaxis, asma, rinitis alérgica, espondilitis anquilosante, polimiositis, dermatomiositis, esclerosis sistémica, artritis idiopática juvenil, polimialgia reumática, enfermedad de Sjogren, histiocitosis de células de Langerhans, enfermedad de Still, enfermedad intestinal inflamatoria, colitis ulcerativa, enfermedad de Crohn, lupus eritematoso sistémico, púrpura trombocitopénica inmune, preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, enfermedad pulmonar obstructiva crónica, enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico, reticulohistiocitosis multicéntrica, hipereosinofilia, y diabetes tipo I con urticaria, diabetes tipo II, insensibilidad a insulina, hiperglucemia, obesidad, y lipólisis, osteoporosis, osteodistrofia, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, osteólisis mediada por infección, y osteólisis peri-prostética o mediada por restos de desgaste, endometriosis, nefritis, necrosis tubular, complicaciones renales asociadas a diabetes, e hipertrofia renal, esclerosis múltiple, síndrome de Charcot Marie Tooth, esclerosis lateral amiotrófica, miastenia grave, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson, dolor agudo, dolor neuropático, dolor inflamatorio, dolor crónico, migraña, mieloma múltiple, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia mieloide crónica, tumores de mastocitos, tumores de mastocitos caninos, cáncer de pulmón, cáncer testicular, cáncer pancreático, cáncer de próstata, cáncer de mama, cáncer ovárico, carcinoma de células de merkel, carcinomas del tracto genital femenino, carcinoma colorectal, carcinoma in situ, tumores de estroma gastrointestinal, angiogénesis tumoral, astrocitoma, neuroblastoma, sarcoma, osteosarcoma, sarcomas de origen neuroectodérmico, tumor de células gigantes de hueso, tumor de células gigantes de vaina tendinosa, sinovitis villonodular pigmentada, melanoma, glioblastoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, neurofibromatosis (incluyendo neoplasia de células de Schwann asociada con

neurofibromatosis), mastocitosis, metástasis de tumores a otros tejidos, metástasis óseas osteolíticas, y otras enfermedades mieloproliferativas crónicas tales como mielofibrosis, enfermedad vascular de la colágena, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fiebre familiar del Mediterráneo, vasculitis de Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu, uveítis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética, querubismo, neurofibromatosis, infecciones asociadas con virus de inmunodeficiencia humana, virus de hepatitis B, virus de hepatitis C, anaplasmosis granulocítica humana, enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick, cirrosis hepática, enfermedad de reflujo gastroesofágico, esofagitis, y úlceras del tracto gastrointestinal, fibrosis pulmonar, lesión pulmonar aguda, cirugía de derivación, cirugía vascular, e injertos vasculares, ateroesclerosis, cardiomiopatía, falla cardiaca, e hipertensión arterial pulmonar. La invención además proporciona uno o más compuestos o composiciones, como se describe en este documento, para su uso para tratar una enfermedad o padecimiento mediado por Fms y mediado por Kit, como se describe en este documento.

[0133] En un vigesimoctavo aspecto, uno o más compuestos, como se describe en este documento, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento seleccionado del grupo que consiste de artritis reumatoide, osteoartritis, osteoporosis, osteólisis peri-prostética, esclerosis sistémica, trastornos desmielinizantes, esclerosis múltiple, síndrome de Charcot Marie Tooth, esclerosis lateral amiotrófica, enfermedad de Alzheimer, enfermedad de Parkinson, colitis ulcerativa, enfermedad de Crohn, púrpura trombocitopénica inmune, preparación de médula ósea para trasplante autólogo, rechazo de trasplantes, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, hipertrofia renal, diabetes tipo I, dolor agudo, dolor inflamatorio, dolor neuropático, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de mama metastásico, cáncer de próstata, cáncer pancreático, cáncer de pulmón, cáncer ovárico, gliomas, glioblastomas, neurofibromatosis, metástasis óseas osteolíticas, metástasis de cerebro, tumores de estroma gastrointestinal, y tumores de células gigantes.

[0134] En un vigesimonoveno aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores de Kit, pueden usarse en la preparación de un medicamento para el tratamiento de artritis reumatoide, tumores de estroma gastrointestinal, melanoma o neurofibromatosis.

[0135] En un trigésimo aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores selectivos de Fms, pueden usarse en la preparación de un medicamento para el tratamiento de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, enfermedad de Parkinson, artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, o hipertrofia renal.

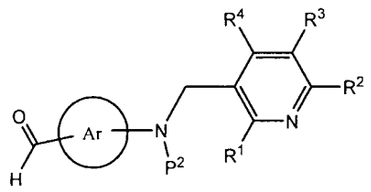
[0136] En un trigésimo primer aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores selectivos de Fms y que cruzan con efectividad la barrera hematoencefálica, pueden usarse en la preparación de un medicamento para el tratamiento de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, o enfermedad de Parkinson.

[0137] En un trigésimo segundo aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores selectivos de Fms y que no cruzan con efectividad la barrera hematoencefálica, pueden usarse en la preparación de un medicamento para el tratamiento de artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, o hipertrofia renal.

[0138] En un trigésimo tercer aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores duales de Fms/Kit, pueden usarse en la preparación de un medicamento para el tratamiento de cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide o esclerosis múltiple.

[0139] En un trigésimo cuarto aspecto, uno o más compuestos, como se describe en este documento, que son inhibidores duales de Fms/Flt-3, pueden usarse en la preparación de un medicamento para el tratamiento de leucemia mieloide aguda.

[0140] En un trigésimo quinto aspecto, la invención proporciona un compuesto intermediario de la Fórmula V:



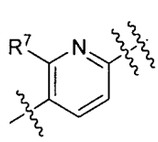
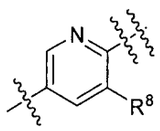
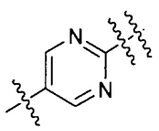
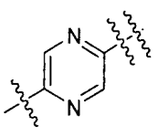
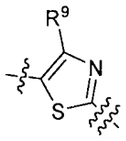
Fórmula V

o un estereoisómero del mismo,

en donde:

P^2 es un grupo protector amino;

Ar se selecciona del grupo que consiste de:

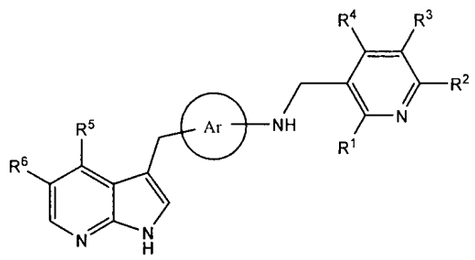
el punto de unión de Ar a -CH_2- de la Fórmula I y en donde  indica el punto de unión de Ar a -NH- de la Fórmula I;

R^1, R^2, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, halógeno, alquilo inferior, alquilo inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{40}, -$S(O)_2$-R^{41}, -$S(O)_2$-N(H)-R^{42}, -N(H)-R^{42}, -$N(R^{42})_2$, y -N(H)-$S(O)_2$-R^{43}, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean –H y uno de R^1, R^2, R^3 y R^4 sea diferente a hidrógeno, en donde:

R^{40} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

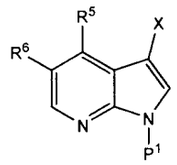
R^{41}, R^{42} y R^{43} son alquilo inferior. En algunas modalidades, las variables Ar, R^7, R^8, R^9, R^1, R^2, R^3 y R^4 son como se define en este documento.

[0141] En un trigésimo sexto aspecto, la invención proporciona un método para preparar un compuesto de la Fórmula I':



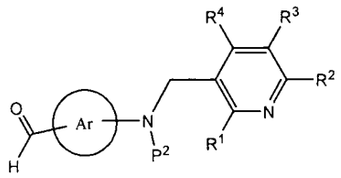
Fórmula I'

El método incluye poner en contacto un compuesto de la Fórmula IV:



Fórmula IV

con un compuesto de la Fórmula V:



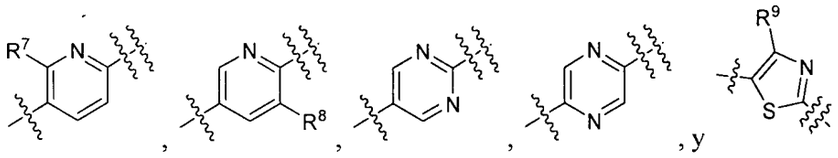
Fórmula V

bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde:

P^1 y P^2 son cada uno independientemente un grupo protector amino;

X es H o un halógeno;

Ar se selecciona del grupo que consiste de:



; en donde  indica el punto de unión de Ar a $-CH_2-$ de la Fórmula I y en donde  indica el punto de unión de Ar a -NH- de la Fórmula I;

R^1, R^2, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, alquilo inferior, alquilo inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, y $-N(H)-S(O)_2-R^{43}$, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean –H y uno de R^1, R^2, R^3 y R^4 sea diferente a hidrógeno, en donde:

R^{40} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{41}, R^{42} y R^{43} son alquilo inferior;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, y $-N(H)-S(O)_2-R^{15}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es H, halógeno o alquilo inferior;

R^8 es H, halógeno, alquilo inferior o alcoxi inferior;

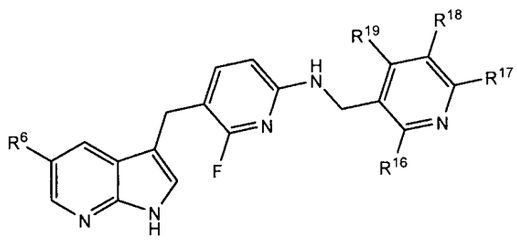
R^9 es H o halógeno;

R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con -O-CH_3, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

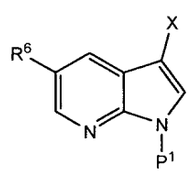
R^{12} y R^{15} son cada uno independientemente alquilo inferior, con la condición de que el compuesto sea diferente a aquel establecido en la Tabla 1. P^1 y P^2 son grupos protectores amino, como se describe en este documento. En una modalidad, P^2 es t-butoxicarbonilo. En otra modalidad, P^1 es fenilsulfonilo. En una modalidad, el contacto se realiza al hacer reaccionar los compuestos de la Fórmula IV con los compuestos de la Fórmula V en presencia de una base fuerte, tal como hidróxido de metal de álcali. Los hidróxidos de metal de álcali ejemplares incluyen NaOH, KOH y LiOH. En otra modalidad, el contacto incluye formar un reactivo de Grignard de los compuestos de la Fórmula IV y además hacer reaccionar el reactivo de Grignard de los compuestos de la Fórmula IV con los compuestos de la Fórmula V. Todavía en otra modalidad, el contacto incluye hacer reaccionar los compuestos de la Fórmula IV con los compuestos de la Fórmula V en presencia de un complejo de paladio. En algunas modalidades, las variables R^5 y R^6 son como se define en cualquiera de las modalidades anteriores para los compuestos de la Fórmula I. En algunas modalidades, las variables R^1, R^2, R^3 y R^4 son como se define en cualquiera de las modalidades anteriores para los compuestos de la Fórmula I.

[0142] En algunas modalidades, la invención proporciona un método para preparar un compuesto de la Fórmula II':



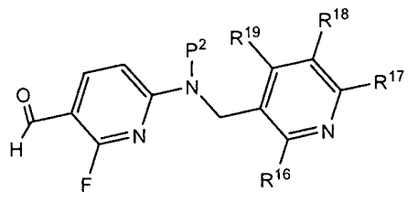
Fórmula II'

El método incluye poner en contacto un compuesto de la Fórmula VI:



Fórmula VI

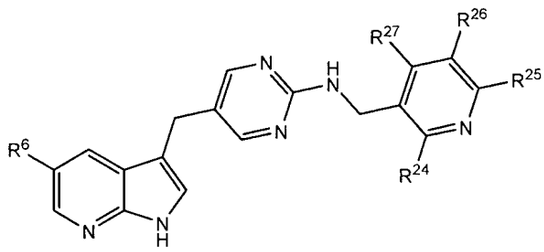
con un compuesto de la Fórmula VII:



Fórmula VII

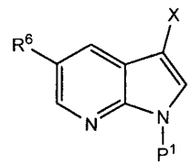
bajo condiciones suficientes para formar el compuesto de la Fórmula II', en donde P^1 y P^2 son cada uno independientemente un grupo protector amino; X es H o un halógeno; R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi. En una modalidad, R^6 es alquilo inferior. En otra modalidad, R^6 es CH_3 o CN. En otra modalidad, R^6 es metilo, etilo o propilo. P^1 y P^2 son grupos protectores amino, como se describe en este documento. En una modalidad, P^2 es t-butoxicarbonilo. En otra modalidad, P^1 es fenilsulfonilo. En una modalidad, el contacto se realiza al hacer reaccionar los compuestos de la Fórmula VI con los compuestos de la Fórmula VII en presencia de una base fuerte, tal como hidróxido de metal de álcali. Los hidróxidos de metal de álcali ejemplares incluyen NaOH, KOH y LiOH. En otra modalidad, el contacto incluye formar un reactivo de Grignard de los compuestos de la Fórmula VI y además hacer reaccionar el reactivo de Grignard de los compuestos de la Fórmula VI con los compuestos de la Fórmula VII.

[0143] En algunas modalidades, la invención proporciona un método para preparar un compuesto de la Fórmula III':



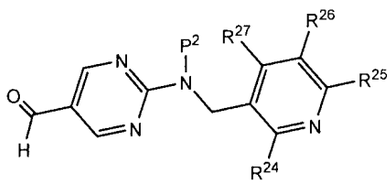
Fórmula III'

El método incluye poner en contacto un compuesto de la Fórmula VI:



Fórmula VI

con un compuesto de la Fórmula VII:



Fórmula VIII

bajo condiciones suficientes para formar el compuesto de la Fórmula II', en donde P^1 y P^2 son cada uno independientemente un grupo protector amino; X es H o un halógeno; R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo. R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi. En una modalidad, R^6 es alquilo inferior. En otra modalidad, R^6 es CH_3 o CN. En otra modalidad, R^6 es metilo, etilo o propilo. P^1 y P^2 son grupos protectores amino, como se describe en este documento. En una modalidad, P^2 es t-butoxicarbonilo. En otra modalidad, P^1 es fenilsulfonilo. En una modalidad, el contacto se realiza al hacer reaccionar los compuestos de la Fórmula VI con los compuestos de la Fórmula VIII en presencia de una base fuerte, tal como hidróxido de metal de álcali. Los hidróxidos de metal de álcali ejemplares incluyen NaOH, KOH y LiOH. En otra modalidad, el contacto incluye formar un reactivo de Grignard de los compuestos de la Fórmula VI y además hacer reaccionar el reactivo de Grignard de los compuestos de la Fórmula VI con los compuestos de la Fórmula VII.

[0144] Aspectos y modalidades adicionales serán obvios a partir de la siguiente Descripción Detallada de la Invención y a partir de las reivindicaciones.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0145] Como se usan en este documento, las siguientes definiciones se aplican a menos que se indique claramente de otra manera:

[0146] Todos los átomos designados dentro de una Fórmula descrita en este documento, ya sea dentro de una estructura proporcionada, o dentro de las definiciones de variables relacionadas con la estructura, pretenden incluir cualquier isótopo de los mismos, a menos que se indique claramente lo contrario. Se entenderá que para cualquier átomo dado, los isótopos pueden presentarse esencialmente en proporciones de acuerdo con su presentación natural, o uno o más átomos particulares pueden aumentarse con respecto a uno o más isótopos usando métodos sintéticos conocidos por un experto en la técnica. De esta manera, el hidrógeno incluye, por ejemplo, ^{1}H, ^{2}H, ^{3}H; carbono incluye, por ejemplo, ^{11}C, ^{12}C, ^{13}C, ^{14}C; oxígeno incluye, por ejemplo, ^{16}O, ^{17}O, ^{18}O; nitrógeno incluye, por ejemplo, ^{13}N, ^{14}N, ^{15}N; azufre 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 similares.

[0147] "Halógeno" o "Halo" se refiere a todos los halógenos, es decir, cloro (Cl), flúor (F), bromo (Br), o yodo (I).

[0148] "Alquilo inferior", solo o en combinación, significa un radical derivado de alcano que contiene de 1 a 6 átomos de carbono (a menos que se defina específicamente) incluyendo un alquilo de cadena lineal o alquilo ramificado. En muchas modalidades, un alquilo inferior es un grupo alquilo lineal o ramificado que contiene de 1-6, 1-4, o 1-2, átomos de carbono, tal como metilo, etilo, propilo, isopropilo, butilo, t-butilo, y similares. Un alquilo inferior puede sustituirse independientemente, como se describe en este documento, a menos que se indique de otra manera, con uno o más, preferentemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, en donde los sustituyentes son como se indica. Además, posibles sustituciones se unen en cualquier átomo disponible para producir un compuesto estable. Por ejemplo "alquilo inferior halo sustituido" denota un grupo alquilo inferior sustituido con uno o más átomos de halógeno, donde preferiblemente el alquilo inferior se sustituye con 1, 2, 3, 4 o 5 átomos de halógeno, también 1, 2, o 3 átomos de halógeno. Además, posibles sustituciones se unen en cualquier átomo disponible para producir un compuesto estable. Por ejemplo "alquilo inferior sustituido con flúor" denota un grupo alquilo inferior sustituido con uno o más átomos de flúor, tal como perfluoroalquilo, donde preferiblemente el alquilo inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. El alquilo inferior sustituido con flúor ejemplar incluye, pero no se limita a, CF_3, CF_2CF_3, CH_2CF_3, y similares. Se entenderá que las sustituciones son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0149] "Alcoxi inferior" se refiere a aquellos grupos alquilo inferior, como se define en este documento, unidos al resto de la molécula mediante un átomo de oxígeno. Grupos alcoxi representativos incluyen metoxi, etoxi, n-propoxi, i-propoxi, n-butoxi, n-pentoxi, n-heptoxi, y similares, así como isómeros de los mismos.

[0150] "Alquenilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) y al menos uno, preferiblemente 1-3, más preferiblemente 1-2, muy preferiblemente uno, doble enlace carbono a carbono. Los dobles enlaces carbono a carbono pueden contenerse dentro de una cadena lineal o porción ramificada. El grupo alquenilo inferior de cadena lineal o ramificado es químicamente factible y se une en cualquier punto disponible para proporcionar un compuesto estable. Ejemplos de grupos alquenilo inferior incluyen etenilo, propenilo, isopropenilo, butenilo, y similares.

[0151] "Alquinilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) que contiene al menos uno, preferiblemente uno, triple enlace carbono a carbono. El grupo alquinilo inferior de cadena lineal o ramificado es químicamente factible y se une en cualquier punto disponible para proporcionar un compuesto estable. Ejemplos de grupos alquinilo incluyen etinilo, propinilo, butinilo, y similares.

[0152] "Cicloalquilo" se refiere a sistemas saturados o insaturados, no aromáticos monocíclicos, bicíclicos o tricíclicos de anillos de carbono de 3-10, también 3-8, más preferiblemente 3-6, miembros de anillo por anillo, tal como ciclopropilo, ciclopentilo, ciclohexilo, adamantilo, y similares.

[0153] "Heterocicloalquilo" se refiere a un grupo cicloalquilo saturado o insaturado no aromático que tiene de 5 a 10 átomos en el cual de 1 a 3 átomos de carbono en el anillo se reemplazan por heteroátomos de O, S o N, y se fusionan opcionalmente con benzo o heteroarilo de 5-6 miembros de anillo. Heterocicloalquilo también pretende incluir S o N oxidado, tal como sulfinilo, sulfonilo y N-óxido de un nitrógeno de anillo terciario. Heterocicloalquilo también pretende incluir compuestos en los cuales un carbono del anillo puede sustituirse con oxo, es decir, el carbono del anillo es un grupo carbonilo, tales como lactonas y lactamas. El punto de unión del anillo heterocicloalquilo está en un átomo de carbono o nitrógeno de tal modo que un anillo estable se retiene. Ejemplos de grupos heterocicloalquilo incluyen, pero no se limitan a, morfolino, tetrahidrofuranilo, dihidropiridinilo, piperidinilo, pirrolidinilo, pirrolidonilo, piperazinilo, dihidrobenzofurilo, y dihidroindolilo.

[0154] "Cicloalquilamino" denota el grupo $-NR^aR^b$, donde R^a y R^b se combinan con el nitrógeno para formar un heterocicloalquilo de 5-7 miembros, donde el heterocicloalquilo puede contener un heteroátomo adicional dentro del anillo, tal como O, N, o S, y también puede sustituirse además con alquilo inferior. Ejemplos de heterocicloalquilo de 5-7 miembros incluyen, pero no se limitan a,

piperidina, piperazina, 4-metilpiperazina, morfolina, y tiomorfolina. Se entenderá que cuando el cicloalquilamino es un sustituyente en otras porciones, estas son químicamente factibles y se unen en cualquier átomo disponible para proporcionar un compuesto estable.

[0155] Como se usa en este documento "Grupo protector" se refiere a un grupo de átomos que, cuando se unen a un grupo reactivo en una molécula, enmascaran, reducen o evitan la reactividad. Ejemplos de grupos protectores pueden encontrarse en T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 4th ed. 2006), Beaucage and Iyer, *Tetrahedron* 48:2223-2311 (1992), y Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Grupos protectores amino representativos incluyen formilo, acetilo, trifluoroacetilo, bencilo, benciloxicarbonilo (CBZ), *ter*-butoxicarbonilo (Boc), trimetil sililo (TMS), 2-trimetilsilil-etanosulfonilo (SES), tritilo y grupos tritilo sustituidos, aliloxicarbonilo, 9-fluorenilmetiloxicarbonilo (FMOC), nitro-veratriloxicarbonilo (NVOC), tri-isopropilsililo (TIPS), fenilsulfonilo y similares (véase también, Boyle, A. L. (Editor), CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, John Wiley and Sons, New York,Volume 1, 2000).

[0156] Como se usa en este documento, "Grupo de salida" tiene el significado convencionalmente asociado con el mismo en química orgánica sintética, es decir, un átomo o grupo capaz de desplazarse por un nucleófilo e incluye halo (tales como cloro, bromo, y yodo), alcanosulfoniloxi, arenosulfoniloxi, alquilcarboniloxi (por ejemplo, acetoxi), arilcarboniloxi, mesiloxi, tosiloxi, trifluorometanosulfoniloxi, ariloxi (por ejemplo, 2,4-dinitrofenoxi), metoxi, N,O-dimetilhidroxilamino, y similares.

[0157] Como se usa en este documento, los términos "tratar", "tratando", "terapia", "terapias", y términos similares se refieren a la administración de material, por ejemplo, uno cualquiera o más compuestos, como se describe en este documento, en una cantidad efectiva para evitar, aliviar, o mejorar uno o más síntomas de una enfermedad o padecimiento, es decir, indicación, y/o para prolongar la supervivencia del sujeto que se trata.

[0158] Como se usa en este documento, el término "enfermedad o padecimiento mediado por proteína cinasa Fms y/o Kit" se refiere a una enfermedad o padecimiento en el cual la función biológica de una proteína cinasa Fms, incluyendo cualquier mutación de la misma, una proteína cinasa Kit, incluyendo cualquier mutación de la misma, o tanto una proteína cinasa Fms como Kit, incluyendo cualquier mutaciones de las mismas, afecta el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento, y/o en el cual la modulación de la proteína cinasa Fms y/o Kit altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. Una enfermedad o padecimiento mediado por proteína cinasa Fms y/o Kit incluye una enfermedad o padecimiento para el cual la modulación proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con

inhibidores de proteína cinasas Fms y/o Kit, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0159] Como se usa en este documento, los términos "enfermedad o padecimiento mediado por proteína cinasa Fms ," "enfermedad o padecimiento mediado por c-fms," y similares se refieren a una enfermedad o padecimiento en el cual la función biológica de una proteína cinasa Fms, incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento, y/o en el cual la modulación de la proteína cinasa Fms altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por proteína cinasas Fms incluye una enfermedad o padecimiento para el cual la inhibición con Fms proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con el o los inhibidores de Fms, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0160] Como se usa en este documento, los términos "enfermedad o padecimiento mediado por proteína cinasa Kit ," "enfermedad o padecimiento mediado por c-kit," y similares se refieren a una enfermedad o padecimiento en el cual la función biológica de una proteína cinasa Kit, incluyendo cualquier mutación de la misma, afecta el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento, y/o en el cual la modulación de la proteína cinasa Kit altera el desarrollo, curso, y/o síntomas de la enfermedad o padecimiento. La enfermedad o padecimiento mediado por proteína cinasas Kit incluye una enfermedad o padecimiento para el cual la inhibición con Kit proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con el o los inhibidores de Kit, incluyendo uno o más compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0161] Como se usa en este documento, el término "inhibidor dual de Fms/Kit " se refiere a un compuesto que inhibe las proteína cinasas Fms y Kit, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms, y que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, en donde la actividad es aproximadamente de igual potencia en cada uno. Los compuestos se consideran aproximadamente de igual potencia si la relación de IC_{50} para la actividad de cinasa Kit dividida entre la IC_{50} para la actividad de cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. Tales compuestos son efectivos para tratar una enfermedad o padecimiento que es una enfermedad o padecimiento mediado ya sea por proteína cinasa Fms o mediado por proteína cinasa Kit o ambas.

Tales compuestos son preferentemente, pero no necesariamente, selectivos con respecto a otras proteína cinasas, es decir, cuando se compara con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la cinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferentemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. Aunque se entenderá que un inhibidor dual de Fms/Kit puede usarse para tratar cualquier enfermedad o padecimiento mediado por proteína cinasa Fms, la inhibición dual de Fms y Kit proporciona efectos beneficiosos para tratar ciertas enfermedades o padecimientos, incluyendo, pero sin limitarse a, cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide o esclerosis múltiple.

[0162] Como se usa en este documento, el término "inhibidor dual de Fms/Flt-3" se refiere a un compuesto que inhibe las proteína cinasas Fms y Flt-3, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms, y que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Flt-3, en donde la actividad es aproximadamente de igual potencia en cada uno. Los compuestos se consideran aproximadamente de igual potencia si la relación de IC_{50} para la actividad de cinasa Flt-3 dividida entre la IC_{50} para la actividad de cinasa Fms está en el intervalo de 20 a 0.05, también 10 a 0.1, también 5 a 0.2. Tales compuestos son efectivos para tratar una enfermedad o padecimiento que es una enfermedad o padecimiento mediado ya sea por proteína cinasa Fms o mediado por proteína cinasa Flt-3 o ambas. Tales compuestos son preferentemente, pero no necesariamente, selectivos con respecto a otras proteína cinasas, es decir, cuando se compara con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la cinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferentemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. Aunque se entenderá que un inhibidor dual de Fms/Flt-3 puede usarse para tratar cualquier enfermedad o padecimiento mediado por proteína cinasa Fms, la inhibición dual de Fms y Flt-3 proporciona efectos beneficiosos para tratar ciertas enfermedades o padecimientos, incluyendo, pero sin limitarse a, leucemia mieloide aguda.

[0163] Como se usa en este documento, el término "inhibidor selectivo de Fms" se refiere a un compuesto que inhibe de manera selectiva la cinasa Fms en relación con la cinasa Kit, es decir, un compuesto que tiene una IC_{50} de menos de 500 nM, menos de 100 nM, menos de 50 nM, menos de 20

nM, menos de 10 nM, menos de 5 nM, o menos de 1 nM cuando se determina en un ensayo generalmente aceptado de actividad de cinasa Fms y, cuando se determina en un ensayo comparable generalmente aceptado de actividad de cinasa Kit, tendrá una relación de IC_{50} para cinasa Kit dividida entre la IC_{50} para cinasa Fms de >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Tales compuestos son efectivos para tratar una enfermedad o padecimiento que está mediado por proteína cinasa Fms, sin afectar la proteína cinasa Kit. Tales compuestos son preferentemente, pero no necesariamente, selectivos con respecto a otras proteína cinasas, es decir, cuando se compara con otra proteína cinasa, la IC_{50} para la otra cinasa dividida entre la IC_{50} para la cinasa Fms es >20, también >30, también >40, también >50, también >60, también >70, también >80, también >90, también >100. Preferentemente, los compuestos son selectivos en relación con otras proteína cinasas incluyendo, pero sin limitarse a, CSK, cinasa del receptor de Insulina, AMPK, PDGFR o VEGFR. Aunque se entenderá que un inhibidor selectivo de Fms puede usarse para tratar cualquier enfermedad o padecimiento mediado por proteína cinasa Fms, la selectividad por Fms proporciona efectos beneficiosos para tratar ciertas enfermedades o padecimientos, incluyendo, pero sin limitarse a, artritis reumatoide, enfermedad de Alzheimer, enfermedad de Parkinson, osteoartritis, nefritis, nefropatía diabética, o hipertrofia renal.

[0164] Como se usa en este documento, el término "barrera hematoencefálica" se refiere a la barrera física en el sistema circulatorio que evita que muchas sustancias, incluyendo ciertos fármacos de molécula pequeña, entren al sistema nervioso central (CNS). Los fármacos que pretenden interactuar con objetivos moleculares en el CNS deben cruzar la barrera hematoencefálica para alcanzar sus objetivos pretendidos. Por el contrario, los agentes que actúan periféricamente no deben cruzar la barrera hematoencefálica para evitar cualquier efecto secundario relacionado con el CNS. La capacidad de un compuesto para penetrar la barrera hematoencefálica se expresa como la permeabilidad de la barrera hematoencefálica o la relación de la concentraciones en estado estacionario del compuesto en el cerebro y en la sangre. La permeabilidad de la barrera hematoencefálica experimental puede medirse por métodos *in vivo*. Diversos métodos pueden emplearse para medir la fracción del compuesto transportado de la sangre al tejido cerebral, incluyendo división de sangre cerebral, perfusión cerebral, índice de captación cerebral, y micro diálisis intracerebral. Sin embargo, estos métodos *in vivo* son laboriosos y de bajo rendimiento en su naturaleza. En la práctica, se usan a menudo métodos computacionales *in silico* para predecir la permeabilidad de la barrera hematoencefálica antes de su confirmación *in vivo*. La mayor parte de los modelos de la barrera hematoencefálica que se han construido hasta ahora se basan en la suposición de que la mayoría de los compuestos se transportan a través de la barrera hematoencefálica por difusión pasiva. De todas las propiedades fisicoquímicas, el área superficial polar (PSA) muestra la mejor correlación con la permeabilidad de la barrera hematoencefálica para compuestos difundidos de manera pasiva. La evidencia empírica sugiere que los compuestos que tienen un área superficial polar

de 100 o mayor típicamente tienen una baja probabilidad de cruzar la barrera hematoencefálica. El área superficial polar se calcula fácilmente a partir de la estructura del compuesto usando un algoritmo publicado (Ertl et al., J. Med. Chem. 2000, 43:3714-3717). Aunque se entenderá que un inhibidor selectivo de Fms puede usarse para tratar cualquier enfermedad o padecimiento mediado por proteína cinasa Fms, los compuestos que cruzan de manera efectiva la barrera hematoencefálica proporcionan efectos beneficiosos para tratar ciertas enfermedades o padecimientos, incluyendo, pero sin limitarse a, esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, y enfermedad de Parkinson, mientras los compuestos que no cruzan de manera efectiva la barrera hematoencefálica proporcionan efectos beneficiosos para tratar ciertas enfermedades o padecimientos, incluyendo, pero sin limitarse a, artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, o hipertrofia renal.

[0165] Como se usa en este documento, el término "forma sólida" se refiere a una preparación sólida (es decir, una preparación que no es gas ni líquido) de un compuesto farmacéuticamente activo que es adecuado para su administración a un sujeto animal pretendido para propósitos terapéuticos. La forma sólida incluye cualquier complejo, tal como una sal, co-cristal o un complejo amorfo, así como cualquier polimorfo del compuesto. La forma sólida puede ser sustancialmente cristalina, semi-cristalina o sustancialmente amorfa. La forma sólida puede administrarse directamente o usarse en la preparación de una composición adecuada que tiene propiedades farmacéuticas mejoradas. Por ejemplo, la forma sólida puede usarse en una formulación que comprende al menos un portador o excipiente farmacéuticamente aceptable.

[0166] Como se usa en este documento, el término material "sustancialmente cristalino" abarca material que tiene más de alrededor de 90% de cristalinidad; y material "cristalino" abarca material que tiene más de alrededor de 98% de cristalinidad.

[0167] Como se usa en este documento, el término material "sustancialmente amorfo" abarca material que tiene no más de alrededor de 10% de cristalinidad; y material "amorfo" abarca material que tiene no más de alrededor de 2% de cristalinidad.

[0168] Como se usa en este documento, el término material "semi-cristalino" abarca material que es mayor a 10% de cristalinidad, pero no más de 90% de cristalinidad; preferiblemente material "semi-cristalino" abarca material que es mayor a 20% de cristalinidad, pero no más de 80% de cristalinidad. En un aspecto de la presente invención, una mezcla de formas sólidas de un compuesto puede prepararse, por ejemplo, una mezcla de formas sólidas amorfas y cristalinas, por ejemplo, para proporcionar una forma sólida "semi-cristalina". Tal forma sólida "semi-cristalina" puede prepararse por métodos conocidos en la técnica, por ejemplo al mezclar una forma sólida amorfa con una forma

sólida cristalina en la proporción deseada. En algunos casos, un compuesto mezclado con ácido o base forma un complejo amorfo; un sólido semi-cristalino puede prepararse empleando una cantidad de componente del compuesto en exceso de la estequiometría del compuesto y ácido o base en el complejo amorfo, lo que resulta en consecuencia en una cantidad del complejo amorfo que se basa en la estequiometría de los mismos, con un compuesto en exceso en forma cristalina. La cantidad de compuesto en exceso usado en la preparación del complejo puede ajustarse para proporcionar la relación deseada de complejo amorfo a compuesto cristalino en la mezcla resultante de formas sólidas. Por ejemplo, donde el complejo amorfo de ácido o base y compuesto tiene una estequiometría 1:1, preparar dicho complejo con una proporción molar 2:1 de compuesto a ácido o base resultará en una forma sólida de 50% de complejo amorfo y 50% de compuesto cristalino. Tal mezcla de formas sólidas puede ser beneficiosa como producto farmacológico, por ejemplo, al proporcionar un componente amorfo que tiene propiedades biofarmacéuticas mejoradas junto con el componente cristalino. El componente amorfo puede estar más fácilmente biodisponible mientras el componente cristalino puede tener una biodisponibilidad retardada. Tal mezcla puede proporcionar exposición rápida y extensa al compuesto activo.

[0169] Como se usa en este documento, el término "complejo" se refiere a una combinación de un compuesto farmacéuticamente activo y una especie molecular adicional que forma o produce una nueva especie química en una forma sólida. En algunos casos, el complejo puede ser una sal, es decir, donde la especie molecular adicional proporciona un contraión ácido/base a un grupo ácido/base del compuesto que resulta en una interacción ácido:base que forma una sal típica. Mientras tales formas de sal típicamente son sustancialmente cristalinas, también pueden ser formas parcialmente cristalinas, sustancialmente amorfas, o amorfas. En algunos casos, la especie molecular adicional, en combinación con el compuesto farmacéuticamente activo, forma un co-cristal no salino, es decir, el compuesto y especie molecular no interactúan a manera de una interacción típica ácido:base, pero aún forma una estructura sustancialmente cristalina. Los co-cristales también pueden formarse a partir de una sal del compuesto y una especie molecular adicional. En algunos casos, el complejo es un complejo sustancialmente amorfo, que puede contener interacciones ácido:base de tipo salino que no forman cristales salinos típicos, pero en lugar de ello forma un sólido sustancialmente amorfo, es decir, un sólido cuyo patrón de difracción en polvo de rayos X no exhibe picos agudos (por ejemplo, exhibe un halo amorfo).

[0170] Como se usa en este documento, el término "estequiometría" se refiere a la proporción molar de dos o más reactantes que se combinan para formar un complejo, por ejemplo, la proporción molar de ácido o base a compuesto que forma un complejo amorfo. Por ejemplo, una mezcla 1:1 de ácido o base con un compuesto (es decir, 1 mol de ácido o base por mol de compuesto) que resulta en una forma sólida amorfa tiene una estequiometría 1:1.

[0171] Como se usa en este documento, el término "composición" se refiere a una preparación farmacéutica adecuada para su administración a un sujeto pretendido para propósitos 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 proporcionar una formulación mejorada del compuesto, tal como un portador o excipiente adecuado.

[0172] Como se usa en este documento, el término "sujeto" se refiere a un organismo viviente que se trata con los compuestos como se describe en este documento, incluyendo, pero sin limitarse a, cualquier mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tal como ganado vacuno, animales de granja tales como caballos, o mascotas tales como perros y gatos.

[0173] Como se usa en este documento, el término "propiedades biofarmacéuticas" se refiere a la acción farmacocinética de un compuesto o complejo de la presente invención, incluyendo la disolución, absorción y distribución del compuesto en la administración a un sujeto. Como tales, ciertas formas sólidas de los compuestos de la invención, tales como complejos amorfos de los compuestos de la invención, pretenden proporcionar una disolución y absorción mejoradas del compuesto activo, que se refleja típicamente en una C_{max} mejorada (es decir, la concentración máxima alcanzada en el plasma después de la administración del fármaco) y AUC mejorada (es decir, área bajo la curva de la concentración plasmática del fármaco vs. tiempo después de la administración del fármaco).

[0174] El término "farmacéuticamente aceptable" indica que el material indicado no tiene propiedades que pueden ocasionar que un médico razonablemente prudente evite la administración del material a un paciente, tomando en consideración la enfermedad o padecimientos a tratarse y la respectiva ruta de administración. Por ejemplo, se requiere comúnmente que tal material sea esencialmente estéril, por ejemplo, para inyectables.

[0175] Ciertos compuestos de la presente invención pueden existir en formas no solvatadas así como formas solvatadas, incluyendo formas hidratadas. "Hidrato" se refiere a un complejo formado por la combinación de moléculas de agua con moléculas o iones del soluto. "Solvato" se refiere a un complejo formado por la combinación de moléculas de solvente con moléculas o iones del soluto. El solvente puede ser un compuesto orgánico, un compuesto inorgánico, o una mezcla de ambos. Solvato pretende incluir 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 abarcan dentro del 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 pretenden estar dentro del alcance de la presente invención.

[0176] En el presente contexto, el término "terapéuticamente efectiva" o "cantidad efectiva" indica que los materiales o cantidad de material es efectiva para prevenir, aliviar, o mejorar uno o más síntomas de una enfermedad o padecimiento médico, y/o para prolongar la supervivencia del sujeto que se trata.

[0177] En el presente contexto, los términos "sinérgicamente efectivo" o "efecto sinérgico" indican que dos o más compuestos que son terapéuticamente efectivos, cuando se usan en combinación, proporcionan efectos terapéuticos mejorados mayores al efecto aditivo que puede esperarse con base en el efecto de cada compuesto usado por sí mismo.

[0178] Por "probar" se quiere decir la creación de condiciones experimentales y la acumulación de datos respecto a un resultado particular de las condiciones experimentales. Por ejemplo, pueden probarse enzimas con base en su capacidad para actuar sobre un sustrato detectable. Un compuesto puede probarse con base en su capacidad para unirse a una molécula o moléculas objetivo particulares.

[0179] Como se usa en este documento, el término "modular" o "modulan" se refiere a un efecto de alterar una actividad biológica, especialmente una actividad biológica asociada con una biomolécula particular tal como una proteína cinasa. Por ejemplo, un inhibidor de una biomolécula particular modula la actividad de esa biomolécula, *por ejemplo*, una enzima, al reducir la actividad de la biomolécula, tal como una enzima. Tal actividad típicamente se indica en cuanto a una concentración inhibitoria (IC_{50}) del compuesto para un inhibidor con respecto, por ejemplo, a una enzima.

[0180] En el contexto del uso, prueba, o selección de los compuestos que son o pueden ser moduladores, el término "contactar" significa que se provoca que el o los compuestos estén en suficiente proximidad a una molécula particular, complejo, célula, tejido, organismo, u otro material especificado que pueden ocurrir interacciones potenciales de unión y/o la reacción química entre el compuesto y otro material especificado.

[0181] "Dolor" o un "padecimiento doloroso" puede ser dolor agudo y/o crónico, incluyendo, sin limitación, aracnoiditis; artritis (por ejemplo, osteoartritis, artritis reumatoide, espondilitis anquilosante, gota); dolor de espalda (por ejemplo, ciática, disco roto, espondilolistesis, radiculopatía); dolor por quemadura; dolor por cáncer; dismenorrea; jaquecas (por ejemplo, migraña,

jaquecas por grupo, jaquecas por tensión); dolor de cabeza y facial (por ejemplo, neuralgia craniana, neuralgia del trigémino); hiperalgesia; hiperpatía; dolor inflamatorio (por ejemplo, dolor asociado con síndrome del intestino irritable, enfermedad intestinal inflamatoria, colitis ulcerativa, enfermedad de Crohn, cistitis, dolor de infección bacteriana, fúngica o viral); formación de tejido queloide o de cicatrización; dolor de labor o parto; dolor muscular (por ejemplo, como resultado de polimiositis, dermatomiositis, miositis por cuerpos de inclusión, lesión repetitiva por estrés (por ejemplo, calambre del escritor, síndrome del túnel carpiano, tendonitis, tenosinovitis)); síndromes de dolor miofascial (por ejemplo, fibromialgia); dolor neuropático (por ejemplo, diabética neuropatía, causalgia, neuropatía por atrapamiento, avulsión del plexo braquial, neuralgia occipital, gota, síndrome de distrofia del reflejo simpático, extremidad fantasma o dolor pos-amputación, neuralgia posherpética, síndrome de dolor central, o dolor de nervios que resulta de trauma (por ejemplo, lesión de nervios), enfermedad (por ejemplo, diabetes, esclerosis múltiple, Síndrome de Guillan-Barre, miastenia grave, enfermedades neurodegenerativas tales como enfermedad de Parkinson, enfermedad de Alzheimer, esclerosis lateral amiotrófica, o tratamiento de cáncer); dolor asociado con trastornos de piel (por ejemplo, zoster, herpes simple, tumores de piel, quistes, neurofibromatosis); lesiones deportivas (por ejemplo, cortes, torceduras, tirones, contusiones, dislocaciones, fracturas, médula espinal, cabeza); estenosis espinal; dolor quirúrgico; alodinia táctil; trastornos temporomandibulares; enfermedad o lesión vascular (por ejemplo, vasculitis, enfermedad de arterias coronarias, lesión por reperfusión (por ejemplo, después de isquemia, apoplejía, o de infartos de miocardio)); otro dolor específico de órganos o tejidos (por ejemplo, dolor ocular, dolor córneo, dolor óseo, dolor de corazón, dolor visceral (por ejemplo, riñón, vesícula biliar, gastrointestinal), dolor de articulaciones, dolor dental, hipersensibilidad pélvica, dolor pélvico, cólico renal, incontinencia urinaria); otro dolor asociado a enfermedad (por ejemplo, anemia de células falciformes, SIDA, herpes zoster, psoriasis, endometriosis, asma, enfermedad pulmonar obstructiva crónica (COPD), silicosis, sarcoidosis pulmonar, esofagitis, acedía, trastorno por reflujo gastroesofágico, úlceras de estómago y duodenal, dispepsia funcional, enfermedad de resorción ósea, osteoporosis, malaria cerebral, meningitis bacteriana); o dolor debido a rechazo injerto v. huésped o rechazos de aloinjertos.

Objetivos de cinasas e indicaciones

[0182] Las proteína cinasas juegan papeles clave en propagar señales bioquímicas en diversas rutas biológicas. Más de 500 cinasas se han descrito, y cinasas específicas se han implicado en una amplia variedad de enfermedades o padecimientos (es decir, indicaciones), incluyendo por ejemplo, sin limitación, cáncer, enfermedad cardiovascular, enfermedad inflamatoria, enfermedad neurológica, y otras enfermedades. Como tales, las cinasas representan importantes puntos de control para la intervención terapéutica con pequeñas moléculas. Proteína cinasas objetivo específicas, es decir cinasa Fms y cinasa Kit, contempladas por la presente invención se describen en la técnica,

incluyendo, sin limitación, como se describe en la Solicitud de Patente Estadounidense Número de Serie 11/473,347 (véase también, publicación PCT WO2007002433), cuya descripción se incorpora por la presente para referencia con respecto a tales objetivos de cinasas, así como lo siguiente:

[0183] **Fms:** Cinasa objetivo Fms (es decir, sarcoma felino de McDonough) es un miembro de la familia de genes originalmente aislados de la cepa Susan McDonough de virus de sarcoma felino. Fms es una tirosina cinasa transmembranal de 108.0 kDa codificada por el cromosoma 5q33.2-q33.3 (símbolo: CSF1R). La estructura del receptor Fms transmembranal comprende dos dominios tipo Ig, un dominio tipo IgC2, dos dominios adicionales tipo Ig, un dominio TM, y el dominio TK.

[0184] Fms es el receptor para el factor estimulante de colonias de macrófagos (M-CSF), y es crucial para el crecimiento y diferenciación del linaje monocito-macrófago. Con la unión de M-CSF al dominio extracelular de Fms, el receptor se dimeriza y trans-autofosforila residuos citoplásmicos de tirosina.

[0185] M-CSF, descrito primero por Robinson y colaboradores (Blood. 1969, 33:396-9), es una citocina que controla la producción, diferenciación, y función de macrófagos. M-CSF estimula la diferenciación de células progenitoras a monocitos maduros, y prolonga la supervivencia de monocitos. Adicionalmente, M-CSF aumenta la citotoxicidad, producción de superóxido, fagocitosis, quimiotaxis, y producción secundaria de citocinas de factores adicionales en monocitos y macrófagos. Ejemplos de tales factores adicionales incluyen factor estimulante de colonias de granulocitos (G-CSF), interleucina-6 (IL-6), e interleucina-8 (IL-8). M-CSF estimula hematopoyesis, promueve diferenciación y proliferación de células progenitoras de osteoclastos, y tiene profundos efectos sobre el metabolismo de lípidos. Adicionalmente, M-CSF es importante en el embarazo. Fisiológicamente, grandes cantidades de M-CSF se producen en la placenta, y se cree que M-CSF juega un papel esencial en la diferenciación de trofoblastos (Motoyoshi, Int J Hematol. 1998, 67:109-22). Los elevados niveles séricos de M-CSF del embarazo temprano pueden participar en los mecanismos inmunológicos responsables para el mantenimiento del embarazo (Flanagan & Lader, Curr Opin Hematol. 1998, 5:181-5).

[0186] La expresión y/o activación aberrante de Fms se ha implicado en leucemia mieloide aguda, AML (Ridge et al, Proc. Nat. Acad. Sci., 1990, 87:1377-1380). Mutaciones en el codón 301 se cree que conducen a transformación neoplásica por independencia del ligando y actividad constitutiva de tirosina cinasa del receptor. El residuo de tirosina en el codón 969 se ha mostrado implicado en una actividad reguladora negativa, que se interrumpe por sustituciones de aminoácidos. Por consiguiente, las mutaciones en Fms son más prevalentes (20%) en leucemia mielomonocítica crónica y AML tipo M4 (23%), las cuales se caracterizan por diferenciación monocítica.

[0187] Un padecimiento relacionado con AML es leucemia mieloide crónica (CML). Durante la crisis blástica mieloide (BC) de CML, no se presentan anormalidades cromosómicas aleatorias adicionales en más de 80% de pacientes. Sin embargo, estas cambios citogenéticos se han reportado precedentes a los signos clínicos de CML-BC por varios meses a años sugiriendo que otros eventos biológicos pueden participar en el proceso de etapas múltiples de la transformación aguda de CML. La producción autócrina de factores de crecimiento se ha mostrado que ocurre en varias malignidades hematológicas y particularmente en AML. Specchia et al [Br J Haematol. 1992 Mar; 80(3):310-6] han demostrado que el gen IL-1 beta se expresa en casi todos los casos de CML en crisis blástica mieloidé, y que una alta proporción de casos mostró expresión constitutiva del gen M-CSF. Muchos de los mismos pacientes en el estudio de Specchia et al demostraron co-expresión simultánea de Fms. Después de la exposición de células leucémicas a acetato miristato de forbol (PMA), la liberación de la proteína M-CSF fue documentada en tres de cinco pacientes estudiados; sin embargo, no se detectó interleucina-3 (IL-3), factor estimulante de colonias de granulocitos y macrófagos (GM-CSF) o factor estimulante de colonias de granulocitos (G-CSF) significativos en estos pacientes. Esto demuestra que diferentes patrones de secreción de factores de crecimiento existen en AML y CML, y que distintos eventos moleculares probablemente se implican en el control de la proliferación leucémica.

[0188] La observación de que la producción de M-CSF, el principal factor de crecimiento de macrófagos, se incrementa en los tejidos durante la inflamación (Le Meur et al, J. Leukocyte Biology. 2002;72:530-537) proporciona un papel para Fms en ciertas enfermedades. Por ejemplo, COPD se caracteriza por limitación de flujo de aire que no es completamente reversible. La limitación de flujo de aire usualmente es progresiva y se asocia con una respuesta inflamatoria anormal de los pulmones a partículas o gases nocivos. La inflamación crónica de COPD se observa a través de las vías respiratorias, parénquima, y vasculatura pulmonar. La población de células inflamatorias consiste de neutrófilos, macrófagos, y linfocitos T, junto con eosinófilos en algunos pacientes. Se postula que los macrófagos juegan un papel orquestante en inflamación por COPD al liberar mediadores tales como TNF-a, IL-8 y LTB4, que son capaces de dañar estructuras pulmonares y/o sostener inflamación neutrofílica.

[0189] Además, la señalización M-CSF/fms es crítica para la formación de osteoclastos y supervivencia de precursores de osteoclastos. Por ejemplo, la pérdida de estrógenos en la menopausia resulta en M-CSF incrementado y de esta manera en número incrementado de osteoclastos y resorción ósea que conduce a riesgo incrementado de fractura y osteoporosis. Por consiguiente, el bloqueo de esta señal es un objetivo para la inhibición de la resorción ósea (Teitelbaum, Science. 2000;289:1504; Rohan, Science. 2000;289:1508).

[0190] La ateroesclerosis, una enfermedad inflamatoria de las paredes de los vasos, se asocia con morbilidad y mortalidad significativa. Un efecto para la inhibición con Fms en el tratamiento y

prevención de ateroesclerosis depende de varias observaciones (Libby, Nature. 2002;420:868-874). Primero, los monocitos residentes en la íntima arterial incrementan la expresión de receptores buscadores e internan lipoproteínas modificadas. Los macrófagos resultantes llevados por lípidos se desarrollan en células de espuma características de la lesión aterosclerótica. Los macrófagos en el ateroma secretan citocinas y factores de crecimiento implicados en la progresión de la lesión. Adicionalmente, los macrófagos se replican dentro de la íntima. A través de Fms, M-CSF activa la transición de monocito a macrófago llevado por lípidos y aumenta la expresión de receptor buscador A. De hecho, las placas ateroscleróticas sobre-expresan M-CSF que es crítica para la progresión aterosclerótica. Los ratones deficientes en M-CSF se ha encontrado que experimentan una ateroesclerosis menos severa que los ratones con M-CSF normal (Rajavashisth, et. al., J. Clin. Invest. 1998;101:2702-2710; Qiao, et. al., Am. J. Path. 1997;150:1687-1699). Por consiguiente, los inhibidores de Fms afectan la señalización de M-CSF, comprometiendo la progresión de monocito a macrófago célula de espuma, supervivencia y replicación de macrófagos, y señalización de citocinas que participa en la progresión de la lesión.

[0191] El papel de M-CSF y Fms en enfisema parece implicar la regulación del metabolismo de elastina a través de control de metaloproteínas de matriz. M-CSF tiene un papel en la modulación de la acumulación y función de macrófagos alveolares (AMs) *in vivo* (Shibata et al, Blood 2001, 98: pp. 2845-2852). Los ratones osteopetróticos (Op/Op) no tienen M-CSF detectable y muestran reducciones variables específicas de tejido en números de macrófagos. Por consiguiente, se supuso que AMs puede disminuirse en número y tiene una función alterada en ratones Op/Op a causa de la ausencia de M-CSF. Shibata et al encontró que macrófagos de pulmón identificados en secciones de pulmón fueron disminuidos en número en ratones Op/Op de 20 días de edad pero no ratones Op/Op mayores a 4 meses en comparación con hallazgos en controles de camada de la misma edad. Los números de AMs recuperados por lavado broncoalveolar (BAL) también se redujeron en ratones Op/Op jóvenes pero no adultos en comparación con controles. De manera importante, los AMs de ratones Op/Op liberaron espontáneamente mayores niveles de metaloproteinasas de matriz (MMPs) que los AMs de los controles. Consistente con una liberación incrementada de MMP, los ratones Op/Op tienen deposición anormal de elastina y espontáneamente desarrollan enfisema en ausencia de evidencia molecular o celular de inflamación pulmonar. Por consiguiente, la modulación de actividad metaloelastasa en macrófagos por M-CSF puede controlar la degradación de fibras de elastina en pulmones o vasos sanguíneos.

[0192] Las células cancerosas metastásicas ocasionan destrucción de hueso, con fractura asociada, dolor, deformación, e hipercalcemia, debido a producción de factores osteoclasticogénicos que incluyen M-CSF por células tumorales (Clohisy et al, Clin. Orthop. 2000, 373: 104-14). La unión de M-CSF al producto Fms estimula la formación de osteoclastos 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 actividad de osteoclastos al nivel de Fms ofrece un objetivo preciso para mejoría de metástasis ósea. Fms también es un objetivo para la mejoría del cáncer de mama metastásico (Lawicki et al., Clin Chim Acta. 2006, Sep, 371(1-2):112-6; Wyckoff et al., Cancer Res. 2007, Mar 15, 67(6):2649-56).

[0193] La nefritis es la inflamación de los riñones. Puede ocasionarse por ejemplo por una infección bacteriana de los riñones o exposición a una toxina. Sin embargo, la nefritis más comúnmente se desarrolla a partir de una reacción inmune anormal, que puede ocurrir, por ejemplo, cuando un anticuerpo ataca el riñón en sí o un antígeno unido a células de riñón, o cuando un complejo antígeno-anticuerpo formado en otra parte en el cuerpo ataca a células en el riñón. Algunos tipos de nefritis implican infiltración de tejidos renales por leucocitos y depósitos de anticuerpos. En otros tipos de nefritis, la inflamación puede consistir de dilatación de tejido o cicatrización sin leucocitos o anticuerpos. Adicionalmente, la nefritis puede ocurrir en cualquier parte en los riñones. Con respecto a los glomérulos, el daño progresivo a los glomérulos ocasiona que la producción de orina falle y los productos metabólicos de desecho se acumulen en la sangre. Cuando el daño a glomérulos es severo, las células inflamatorias y células glomerulares dañadas se acumulan, comprimiendo los capilares dentro del glomérulo e interfiriendo con la filtración. La cicatrización puede desarrollarse, impedir la función renal y reducir la producción de orina. En algunos casos, pueden formarse microtrombos en los pequeños vasos sanguíneos, disminuyendo además la función renal. Menos comúnmente, la nefritis implica los tejidos tubulointersticiales; tal inflamación se llama tubulonefritis intersticial. Cuando la inflamación daña los túbulos y los tejidos tubulointersticiales, los riñones pueden volverse incapaces de concentrar la orina, eliminar (excretar) productos metabólicos de desecho del cuerpo, o balancear la excreción de sodio y otros electrolitos, tal como potasio. Cuando los túbulos y tejidos tubulointersticiales se dañan, a menudo se desarrolla falla renal. Por consiguiente, la inhibición de Fms ofrece un objetivo para la intervención terapéutica en nefritis debido a la modulación de la respuesta inflamatoria que comprende la etiología de la enfermedad.

[0194] La nefritis por Lupus, es decir, la implicación renal en lupus eritematoso sistémico (SLE), es una manifestación de enfermedad común con un pobre pronóstico. Al menos tres mecanismos inmuno-patogénicos potencialmente superpuestos, para nefritis por lupus se soportan por datos experimentales. Primero, complejos inmunes circulantes que consisten principalmente de DNA y anti-DNA se depositan en el riñón. La activación del complemento resultante y quimiotaxis de neutrófilos conduce a un proceso inflamatorio local. Segundo, la formación in situ de complejos de antígeno y anticuerpo de manera similar puede conducir a activación del complemento y lesión mediada por leucocitos. Tercero, los anticuerpos contra objetivos celulares específicos pueden producir lesión renal. Un mecanismo adicional se observa en pacientes SLE con el síndrome de

anticuerpos antifosfolípidos. La trombosis glomerular puede resultar de la hipercoagulabilidad que acompaña a los anticuerpos dirigidos contra complejos fosfolípido-proteína negativamente cargados (por ejemplo, VDRL falso positivo biológico, anticuerpos anticardiolipina, y anticoagulante de lupus). La nefritis del mesangio por lupus se acompaña por hallazgos diagnósticos normales o con un grado moderado de proteinuria pero típicamente ausencia de hipertensión o sedimento urinario anormal. La glomerulonefritis focal y difusa proliferativa por lupus a menudo se asocia con el peor pronóstico para supervivencia renal y puede acompañarse por síndrome nefrótico, hipertensión significativa y sedimento anormal de orina. La nefritis membranosa por lupus a menudo se presenta con proteinuria, de moderado a alto grado, pero usualmente sedimento urinario normal en ausencia de hipertensión. La nefropatía por lupus del mesangio generalmente se asocia con un excelente pronóstico, mientras que la nefropatía proliferativa por lupus, especialmente variante difusa, a menudo se caracteriza por hipertensión, formaciones de eritrocitos y deterioro significativo de la función renal. El síndrome nefrótico en ausencia de hipertensión, sedimento urinario activo o hipocomplementemia significativa sugieren la variante membranosa de nefropatía por lupus. La nefropatía membranosa generalmente se asocia con un buen pronóstico y relativa conservación de la función renal. Sin embargo, en presencia de proteinuria de intervalo nefrótico persistente, la nefropatía membranosa por lupus puede, de hecho, conducir a pérdida de función renal y enfermedad renal de fase terminal (ESRD). Por consiguiente, la inhibición de Fms ofrece un objetivo para la intervención terapéutica en lupus debido a la modulación de la respuesta inflamatoria que comprende la etiología de la enfermedad.

[0195] La acumulación de macrófagos es un rasgo prominente en muchas formas de glomerulonefritis. La proliferación local de macrófagos dentro del riñón se ha descrito en glomerulonefritis humana y experimental y puede tener un importante papel en aumentar la respuesta inflamatoria. Isbel et al (Nefrol Dial Transplant 2001, 16: 1638-1647) examinó la relación entre proliferación local de macrófagos y expresión renal de M-CSF. La expresión glomerular y tubulointersticial de M-CSF se encontró sobre-regulada en glomerulonefritis humana, siendo más prominente en formas proliferativas de enfermedad. Dado que esto correlaciona con proliferación local de macrófagos, sugiere que la producción renal incrementada de M-CSF juega un importante papel en regular la proliferación local de macrófagos en glomerulonefritis humana. En un modelo de inflamación renal (UUO- obstrucción uretérica unilateral) el tratamiento con anticuerpos anti-Fms redujo la acumulación de macrófagos (Le Meur et.al., J Leukocyte Biology, 2002, 72: 530-537). Por consiguiente, la inhibición de Fms ofrece un objetivo para la intervención terapéutica en glomerulonefritis.

[0196] La insensibilidad a insulina y obesidad son rasgos notables de diabetes tipo II y hay una fuerte correlación entre insensibilidad a insulina y acumulación de grasa visceral abdominal (Bjorntrop, Diabetes Metab. Res. Rev., 1999, 15: 427-441). La evidencia actual indica que los

macrófagos que se acumulan en tejido adiposo liberan TNF-a y otros factores que ocasionan cambios en los adipocitos (hipertrofia, lipólisis, sensibilidad reducida a insulina) y también promueven la insensibilidad a insulina en tejidos circundantes. Por lo tanto, la acumulación de macrófagos en diabetes tipo 2 es importante para progresión de la enfermedad. Por consiguiente, la inhibición de Fms tiene potencial en prevenir el desarrollo de insensibilidad a insulina e hiperglucemia.

[0197] De manera similar, la observación de que la producción de M-CSF, el principal factor de crecimiento de macrófagos, se incrementa en los tejidos durante la inflamación destaca un papel para Fms en enfermedades, tales como por ejemplo enfermedades inflamatorias. Más particularmente, dado qué elevados niveles de M-CSF se encuentran en el estado de enfermedad, la modulación de la actividad de Fms puede mejorar la enfermedad asociada con niveles incrementados de M-CSF.

[0198] Un inhibidor de Fms puede ser útil para tratar indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, artritis reumatoide, osteoartritis, artritis psoriática, 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, síndrome inflamatorio intestinal, colitis ulcerativa, enfermedad de Crohn, lupus eritematoso sistémico (SLE), rechazo de trasplantes, enfermedad pulmonar obstructiva crónica (COPD), enfisema, Enfermedad de Kawasaki, síndrome hemofagocítico (síndrome de activación de macrófagos), reticulohistiocitosis multicéntrica, y ateroesclerosis; trastornos metabólicos, incluyendo, pero sin limitarse a, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, obesidad, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo, pero sin limitarse a, osteoporosis, osteodistrofia, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, osteólisis mediada por infección (por ejemplo, osteomielitis), y osteólisis peri-prostética o mediada por restos de desgaste; enfermedades renales y genitourinarias, incluyendo, pero sin limitarse a, endometriosis, nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia renal; trastornos del sistema nervioso central, incluyendo, pero sin limitarse a, esclerosis múltiple, esclerosis lateral amiotrófica (ALS), miastenia grave, polineuropatía desmielinizante crónica, otros trastornos desmielinizantes, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson; dolor inflamatorio y crónico, incluyendo, pero sin limitarse a, dolor óseo; malignidades, incluyendo, pero sin limitarse a, mieloma múltiple, leucemia mieloide aguda (AML), leucemia mieloide crónica (CML), cáncer de pulmón, cáncer pancreático, cáncer de próstata, cáncer de mama, cáncer ovárico, neuroblastoma, sarcoma, osteosarcoma, tumor de células gigantes de hueso, tumor de células gigantes de vaina tendinosa (TGCT), sinovitis villonodular pigmentada (PVNS), angiogénesis tumoral, melanoma, glioblastoma multiforme, glioma, otros tumores del sistema nervioso central, metástasis de tumores a

otros tejidos, y otras enfermedades mieloproliferativas crónicas tales como mielofibrosis; vasculitis, incluyendo, pero sin limitarse a, enfermedad vascular de la colágena, poliarteritis nodosa, enfermedad de Behcet, sarcoidosis, fiebre familiar del Mediterráneo, vasculitis de Churg-Strauss, arteritis temporal, arteritis de células gigantes, arteritis de Takayasu; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis, escleritis, retinitis, degeneración macular relacionada con la edad, neovascularización coroidea, retinopatía diabética; trastornos heredados, incluyendo, pero sin limitarse a, querubismo, neurofibromatosis; indicaciones de enfermedades infecciosas, incluyendo, pero sin limitarse a, infecciones asociadas con virus de inmunodeficiencia humana, virus de hepatitis B, virus de hepatitis C, anaplasmosis granulocítica humana; trastornos de almacenamiento lisosómico, incluyendo, pero sin limitarse a, enfermedad de Gaucher, enfermedad de Fabry, enfermedad de Niemann-Pick; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, cirrosis hepática; indicaciones pulmonares, incluyendo, pero sin limitarse a, fibrosis pulmonar, lesión pulmonar aguda (por ejemplo, inducida por ventilador, inducida por fumar o por toxinas); e indicaciones quirúrgicas, incluyendo, pero sin limitarse a, cirugía de derivación (cardiopulmonar), cirugía vascular, e injertos vasculares.

[0199] **Kit:** Cinasa objetivo Kit (es decir, oncogen de sarcoma viral felino Hardy-Zuckerman 4) es una tirosina cinasa transmembranal de 109.9 kDa codificada por el cromosoma 4q12 (símbolo: KIT). Las proteína tirosina cinasas receptoras (RPTKs) regulan cascadas clave de transducción de señales que controlan crecimiento y proliferación celular. El receptor Kit del Factor de Células Madre (SCF) es una RPTK transmembranal tipo III que incluye cinco dominios extracelulares de inmunoglobulina (IG), un solo dominio transmembranal, y un dominio dividido de cinasa citoplásmico separado por un segmento de inserto de cinasa. Kit juega un importante papel en el desarrollo de melanocitos, mastocitos, células germinales, y hematopoyéticas.

[0200] El Factor de Células Madre (SCF) es una proteína codificada por el locus S1, y también se ha llamado ligando de kit (KL) y factor de crecimiento de mastocitos (MGF), con base en las propiedades biológicas usadas para identificarlo (revisado en Tsujimura, Patol Int 1996, 46:933-938; Loveland, et al., J. Endocrinol 1997, 153:337-344; Vliagoftis, et al., Clin Inmunol 1997, 100:435-440; Broudy, Blood 1997, 90:1345-1364; Pignon, Hermatol Cell Ther 1997, 39:114-116; y Lyman, et al., Blood 1998, 91:1101-1134.). En este documento la abreviatura SCF se refiere al ligando para Kit.

[0201] SCF se sintetiza como una proteína transmembranal con un peso molecular de 220 o 248 Daltones, dependiendo de la edición alternativa del mRNA para codificar el exón 6. La proteína mayor puede escindirse proteolíticamente para formar una proteína glucosilada soluble, que se dimeriza de manera no covalente. Las formas soluble y unida a membrana de SCF pueden unirse y activar a Kit. Por ejemplo, en la piel, SCF se expresa predominantemente por fibroblastos, queratinocitos, y células endoteliales, que modulan la actividad de melanocitos y mastocitos que

expresan Kit. En médula ósea las células de estroma expresan SCF y regulan la hematopoyesis de células madre que expresan Kit. En el tracto gastrointestinal, las células epiteliales intestinales expresan SCF y afectan las células intersticiales de Cajal y linfocitos intraepiteliales. En los testículos, las células de sertoli y células de la granulosa expresan SCF que regula la espermatogénesis por interacción con Kit en células germinales.

[0202] De acuerdo con OMIM, la señalización desde Kit es esencial para el crecimiento de células germinales primordiales *in vivo* e *in vitro*. Muchos efectores corriente abajo de la ruta de señalización de KIT se han identificado en otros tipos de células, pero se desconoce cómo estas moléculas controlan supervivencia y proliferación de células germinales primordiales. La determinación de los efectores de KIT que actúan en células germinales primordiales se ha impedido por la carencia de métodos efectivos para manipular fácilmente la expresión génica en estas células. De Miguel et al. (2002) superaron este problema al probar la eficacia de la transferencia génica mediada por retrovirus para manipular la expresión génica en células germinales de mamífero. Encontraron que las células germinales primordiales pueden infectarse con éxito con una diversidad de tipos de retrovirus. Usaron este método para demostrar un importante papel de la AKT1 en regular el crecimiento de células germinales primordiales (OMIM MIM Número: **164920**: 04/17/2006).

[0203] La expresión y/o activación aberrante de Kit se ha implicado en una diversidad de estados patológicos. Por ejemplo, la evidencia para una contribución de Kit a la patología neoplásica incluye su asociación con leucemias y tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, y algunos cánceres del tracto gastrointestinal y sistema nervioso central. Además, Kit se ha implicado en jugar un papel en carcinogénesis de los sarcomas del tracto genital femenino de origen neuroectodérmico, y neoplasia de células de Schwann asociada con neurofibromatosis. Se encontró que los mastocitos se implican en modificar el microambiente tumoral y aumentar el crecimiento de tumores (Yang et al., J Clin Invest. 2003, 112:1851-1861; Viskochil, J Clin Invest. 2003, 112:1791-1793). Los inihibitors de Kit también pueden usarse para orientarse a melanoma (Smalley et al., Histol Histopathol. 2009, May, 24(5):643-50), tumores de estroma gastrointestinal (Demetri, GD, Semin Oncol. 2001, Oct, 28(5 Suppl 17):19-26), neurofibromatosis (Yang et al., Cell, 2008, Oct 31, 135(3):437-48), y esclerosis múltiple (Secor et al., J Exp Med. 2000, Mar 6, 191(5):813-22).

[0204] Un inhibidor de Kit puede ser útil para tratar malignidades, incluyendo, pero sin limitarse a, tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas (NSCLC), cáncer testicular, cáncer pancreático, cáncer de mama, carcinoma de células de merkel, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, tumores de estroma gastrointestinal (GISTs), angiogénesis tumoral, glioblastoma, astrocitoma, neuroblastoma, neurofibromatosis (incluyendo neoplasia de células de Schwann asociada con neurofibromatosis), leucemia mielocítica aguda, leucemia linfocítica aguda,

leucemia mielógena crónica, mastocitosis, melanoma, y tumores de mastocitos caninos; enfermedad cardiovascular, incluyendo, pero sin limitarse a, ateroesclerosis, cardiomiopatía, falla cardiaca, hipertensión arterial pulmonar y fibrosis pulmonar; indicaciones inflamatorias y autoinmunes, incluyendo, pero sin limitarse a, alergia, anafilaxia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome intestinal inflamatorio, rechazo de trasplantes, hipereosinofilia, urticaria y dermatitis; indicaciones gastrointestinales, incluyendo, pero sin limitarse a, enfermedad de reflujo gastroesofágico (GERD), esofagitis, y úlceras del tracto gastrointestinal; indicaciones oftálmicas, incluyendo, pero sin limitarse a, uveítis y retinitis; e indicaciones neurológicas, incluyendo, pero sin limitarse a, migraña.

[0205] **Flt3:** Cinasa objetivo Flt3 (es decir, tirosina cinasa 3 similar a Fms) es una tirosina cinasa transmembranal de 112.8 kDa codificada por el cromosoma 13q12 (símbolo: FLT3). De acuerdo con OMIM, Rosnet et al. (*Genomics 1991,* 9: 380-385) aislaron un miembro novedoso de los receptores clase 3 discutidos anteriormente. Demostraron que este gen de la familia de tirosina cinasas, llamado FLT3, tiene fuertes similitudes de secuencia con otros miembros del grupo. Las células madre linfohematopoyéticas sirven como depósito para virtualmente todas las células de la sangre pero constituyen sólo aproximadamente 0.01% de las células de la médula humana o murina. La capacidad para aislar y expandir esta población tiene aplicaciones clínicas en trasplantes de médula ósea para cáncer y enfermedades genéticas. Small et al. (*Proc. Nat. Acad. Sci.* 1994, 91: 459-463) clonaron el cDNA para tirosina cinasa 1 de células madre, el homólogo humano de Flk2/Flt3 murino, a partir de un genoteca rica en células madre hematopoyéticaCD34+. El cDNA codificaba una proteína de 993 aminoácidos con 85% de identidad y 92% de similitud con el homólogo murino. STK1, que es idéntica a FLT3, es un miembro de la familia de tirosina cinasas de receptor tipo III que incluye KIT, FMS, y al receptor del factor de crecimiento derivado de plaquetas. La expresión de STK1 en sangre humana y médula se restringe a las cells CD34+, una población enriquecida en gran medida por células madre/progenitoras. Los oligonucleótidos antisentido dirigidos contra secuencias de STK1 inhibieron la formación de colonias hematopoyéticas, más fuertemente en cultivos de largo plazo de médula ósea. Los datos sugirieron que STK1 puede funcionar como receptor del factor de crecimiento en células madre hematopoyéticas y/o progenitoras (OMIM MIM Number: **136351**: 03/03/2005).

[0206] Levis et al., declaran que mutaciones internas por duplicación en tándem (ITD) de la tirosina cinasa FLT3 de receptor se han encontrado en 20% a 30% de pacientes con leucemia mieloide aguda (AML). Estas mutaciones activan de manera constitutiva al receptor y parecen asociarse con un mal pronóstico. En su estudio, ensayos citotóxicos de dosis-respuesta se realizaron con AG1295, un inhibidor de tirosina cinasas activo contra FLT3, en células primarias de pacientes con AML, y encontraron que AG1295 era específicamente citotóxico para células AML que llevan mutaciones en FLT3/ITD. Sugieren que estas mutaciones contribuyen al proceso leucémico y que el receptor FLT3

representa un objetivo terapéutico en AML (Levis et al., Blood 2001, 98:885-887). Un inhibidor de Flt3 puede ser útil para tratar la leucemia mieloide aguda, síndrome mielodisplásico, leucemia linfoblástica aguda.

Ensayos de Actividad Cinasa

[0207] Una serie de diferentes ensayos para actividad de cinasa puede utilizarse para probar los moduladores activos y/o determinar especificidad de un modulador para una cinasa particular o grupo de cinasas. Además de los ensayos mencionados en los Ejemplos en lo siguiente, alguien con experiencia ordinaria en la técnica puede identificar fácilmente otros ensayos que pueden utilizarse y podrá modificar un ensayo para una aplicación particular. Por ejemplo, numerosos artículos concernientes a cinasas describen ensayos que pueden usarse.

[0208] Ensayos alternativos adicionales pueden emplear determinaciones de unión. Por ejemplo, esta clase de ensayo puede formatearse en un formato de transferencia de energía por resonancia de fluorescencia (FRET), o usando un formato AlfaScreen (*e*nsayo *h*omogéneo de *p*roximidad *l*uminiscente *a*mplificada) al variar los reactivos donador y aceptor que se unen a estreptavidina o el anticuerpo específico de fósforo.

Técnicas Sintéticas Orgánicas

[0209] Una amplia diversidad de técnicas sintéticas orgánicas existen en el arte para facilitar la construcción de moduladores potenciales. Muchos de estos métodos sintéticos orgánicos se describen en detalle en fuentes de referencia estándar utilizadas por los expertos en la técnica. Un ejemplo de tal referencia es March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. De esta manera, las técnicas útiles para sintetizar un modulador potencial de la función de cinasa se encuentran fácilmente disponibles para los expertos en la técnica de síntesis química orgánica.

Formas o Derivados de Compuestos Alternativos

[0210] Los compuestos contemplados en este documento se describen con referencia a fórmulas genéricas y compuestos específicos. Además, los compuestos de la invención pueden existir en una serie de diferentes formas o derivados, todos dentro del alcance de la presente invención. Formas o derivados alternativos, incluyen, por ejemplo, (a) profármacos, y metabolitos activos (b) tautómeros, isómeros (incluyendo estereoisómeros y regioisómeros), y mezclas racémicas (c) sales farmacéuticamente aceptables y (d) formas sólidas, incluyendo diferentes formas cristalinas, sólidos polimórficos o amorfos, incluyendo hidratos y solvatos de los mismos, y otras formas.

(a) Profármacos y Metabolitos

[0211] Además de las presentes fórmulas y compuestos descritos en este documento, la invención también incluye profármacos (generalmente profármacos farmacéuticamente aceptables), derivados metabólicos activos (metabolitos activos), y sus sales farmacéuticamente aceptables.

[0212] Los profármacos son compuestos o sales farmacéuticamente aceptables de los mismos que, cuando se metabolizan bajo condiciones fisiológicas o cuando se convierten por solvólisis, producen el compuesto activo deseado. Los profármacos incluyen, sin limitación, ésteres, amidas, carbamatos, carbonatos, ureidos, solvatos, o hidratos del compuesto activo. Típicamente, el profármaco es inactivo, o menos activo que el compuesto activo, pero puede proporcionar una o más propiedades favorables de manejo, administración, y/o metabólicas. Por ejemplo, algunos profármacos son ésteres del compuesto activo; durante la metabólisis, el grupo éster se escinde para producir el fármaco activo. Los ésteres incluyen, por ejemplo, ésteres de un grupo ácido carboxílico, o derivados S-acilo o O-acilo de grupos tiol, alcohol, o fenol. En este contexto, un ejemplo común es un alquiléster de un ácido carboxílico. Los profármacos también pueden incluir variantes en donde un grupo -NH del compuesto se ha sometido a acilación, tal como la posición 7 del anillo pirrolo[2,3-d]pirimidina o la posición 1 del anillo 1H-pirrolo[2,3-b]piridina de los compuestos, como se describe en este documento, donde la escisión del grupo acilo proporciona el grupo libre -NH del fármaco activo. Algunos profármacos se activan enzimáticamente para producir el compuesto activo, o un compuesto puede someterse a una reacción química posterior para producir el compuesto activo. Los profármacos pueden proceder de forma profármaco a forma activa en una sola etapa o pueden tener una o más formas intermedias que pueden tener por sí mismas actividad o pueden ser inactivas.

[0213] Como se describe en *The Practice of Medicinal Chemistry*, Cap. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, profármacos bioprecursores y profármacos portadores. Generalmente, los profármacos bioprecursores son compuestos que son inactivos o tienen baja actividad en comparación con el compuesto farmacológico activo correspondiente, que contiene uno o más grupos protectores y se convierten a una forma activa por metabolismo o solvólisis. La forma farmacológica activa y cualesquier productos metabólicos liberados deben tener toxicidad aceptablemente baja. Típicamente, la formación de compuesto farmacológico activo implica un proceso o reacción metabólica que es uno de los siguientes tipos:

[0214] Reacciones Oxidativas: Las reacciones oxidativas se ejemplifican sin limitación por reacciones tales como oxidación de funcionalidades alcohol, carbonilo, y ácido, hidroxilación de carbonos alifáticos, hidroxilación de átomos de carbono alicíclico, oxidación de átomos de carbono aromático, oxidación de dobles enlaces carbono-carbono, oxidación de grupos funcionales que contienen nitrógeno, oxidación de silicio, fósforo, arsénico, y azufre, N-desalquilación oxidativa, O- y S-desalquilación oxidativa, desaminación oxidativa, así como otras reacciones oxidativas.

[0215] Reacciones reductoras: Las reacciones reductoras se ejemplifican sin limitación por reacciones tales como reducción de funcionalidades carbonilo, reducción de funcionalidades alcohol y dobles enlaces carbono-carbono, reducción de grupos funcionales que contienen nitrógeno, y otras reacciones de reducción.

[0216] Reacciones sin cambio en el estado de oxidación: Las reacciones sin cambio en el estado de oxidación se ejemplifican sin limitación a reacciones tales como hidrólisis de ésteres y éteres, escisión hidrolítica de enlaces sencillos carbono-nitrógeno, escisión hidrolítica de heterociclos no aromáticos, hidratación y deshidratación en múltiples enlaces, nuevos enlaces atómicos que resultan de reacciones de deshidratación, deshalogenación hidrolítica, remoción de molécula de haluro de hidrógeno, y otras reacciones semejantes.

[0217] Los profármacos portadores son compuestos farmacológicos que contienen una porción de transporte, por ejemplo, que mejora la asimilación y/o suministro localizado a un sitio o sitios de acción. De manera deseable para tal profármaco portador, el enlace entre la porción farmacológica y la porción de transporte es un enlace covalente, el profármaco es inactivo o menos activo que el compuesto farmacológico, el profármaco y cualquier porción de transporte de liberación son aceptablemente no tóxicos. Para profármacos donde la porción de transporte pretende aumentar la asimilación, típicamente la liberación de la porción de transporte debe ser rápida. En otros casos, es deseable utilizar una porción que proporciona liberación lenta, por ejemplo, ciertos polímeros u otras porciones, tales como ciclodextrinas. (Véase, por ejemplo, Cheng et al., Publ. de Patente Estadounidense No. 20040077595, Solic. No. 10/656,838, incorporada en este documento para referencia). Tales profármacos portadores son a menudo favorables para los fármacos administrados en forma oral. En algunos casos, la porción de transporte proporciona un suministro orientado del fármaco, por ejemplo el fármaco puede conjugarse a un anticuerpo o fragmento de anticuerpo. Los profármacos portadores pueden, por ejemplo, usarse para mejorar una o más de las siguientes propiedades: lipofilicidad incrementada, duración incrementada de efectos farmacológicos, especificidad incrementada de sitio, toxicidad y reacciones adversas reducidas, y/o mejora en formulación farmacológica (por ejemplo, estabilidad, solubilidad en agua, depresión de una propiedad organoléptica o fisioquímica indeseable). Por ejemplo, la lipofilicidad puede incrementarse por esterificación de grupos hidroxilo con ácidos carboxílicos lipofílicos, o de grupos ácido carboxílico con alcoholes, por ejemplo, alcoholes alifáticos. Wermuth, *supra*.

[0218] Los metabolitos, por ejemplo, metabolitos activos, se superponen con los profármacos como se describe antes, por ejemplo, profármacos bioprecursores. De esta manera, tales metabolitos son compuestos farmacológicamente activos o compuestos que se metabolizan además a compuestos farmacológicamente activos que son derivados resultantes de procesos metabólicos en el cuerpo de un sujeto. De estos, los metabolitos activos son tales compuestos derivados farmacológicamente activos.

Para profármacos, el compuesto profarmacológico generalmente es inactivo o de actividad inferior al producto metabólico. Para metabolitos activos, el compuesto original puede ser un compuesto activo o puede ser un profármaco inactivo. Por ejemplo, en algunos compuestos, uno o más grupos alcoxi pueden metabolizarse a grupos hidroxilo mientras se retiene actividad farmacológica y/o pueden esterificarse grupos carboxilo, por ejemplo, glucuronidación. En algunos casos, puede haber más de un metabolito, donde un metabolito o metabolitos intermediarios se metaboliza además para proporcionar un metabolito activo. Por ejemplo, en algunos casos un compuesto derivado que resulta de glucuronidación metabólica puede ser inactivo o de baja actividad, y además puede metabolizarse para proporcionar un metabolito activo.

[0219] Los metabolitos de un compuesto pueden identificarse usando técnicas de rutina conocidas en el arte, y sus actividades determinarse usando pruebas tales como aquellas descritas en este documento. Véase, por ejemplo, Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev.* Res., 34:220-230; Wermuth, *supra*.

(b) Tautómeros, Estereoisómeros, y Regioisómeros

[0220] Se entiende que algunos compuestos pueden exhibir tautomerismo. En tales casos, las fórmulas proporcionadas en este documento representan expresamente sólo una de las posibles formas tautoméricas. Por lo tanto debe entenderse que las fórmulas proporcionadas en este documento pretenden representar cualquier forma tautomérica de los compuestos representados y no deben limitarse meramente a la forma tautomérica específica representada por los dibujos de las fórmulas.

[0221] Asimismo, algunos de los compuestos de acuerdo con la presente invención pueden existir como estereoisómeros, es decir, que tienen la misma conectividad atómica de átomos enlazados de manera covalente que difieren todavía en la orientación espacial de los átomos. Por ejemplo, los compuestos pueden ser estereoisómeros ópticos, que contienen uno o más centros quirales, y por lo tanto, pueden existir en dos o más formas estereoisoméricas (por ejemplo, enantiómeros o diastereómeros). De esta manera, tales compuestos pueden presentarse como estereoisómeros únicos (es decir, esencialmente libres de otros estereoisómeros), racematos, y/o mezclas de enantiómeros y/o diastereómeros. Como otro ejemplo, los estereoisómeros incluyen isómeros geométricos, tal como orientación *cis-* o *trans-* de sustituyentes en carbonos adyacentes de un doble enlace. Todos los estereoisómeros únicos semejantes, racematos y mezclas de los mismos pretenden estar dentro del alcance de la presente invención. A menos que se especifique lo contrario, todas las formas estereoisoméricas semejantes se incluyen dentro de las fórmulas proporcionadas en este documento.

[0222] En algunas modalidades, un compuesto quiral de la presente invención está en una forma que contiene al menos 80% de un solo isómero (60% de exceso enantiomérico ("e.e.") o exceso

diastereomérico ("d.e.")), o al menos 85% (70% de e.e. o d.e.), 90% (80% de e.e. o d.e.), 95% (90% de e.e. o d.e.), 97.5% (95% de e.e. o d.e.), o 99% (98% de e.e. o d.e.). Como se entiende generalmente por los expertos en la técnica, un compuesto ópticamente puro que tiene un centro quiral es uno que consiste esencialmente de uno de los dos posibles enantiómeros (es decir, es enantioméricamente puro), y un compuesto ópticamente puro que tiene más de un centro quiral es uno que es diastereoméricamente puro y enantioméricamente puro. En algunas modalidades, el compuesto se presenta en forma ópticamente pura, tal forma ópticamente pura preparándose y/o aislándose por métodos conocidos en la técnica (por ejemplo, por técnicas de recristalización, técnicas sintéticas quirales (incluyendo síntesis a partir de materiales de inicio ópticamente puros), y separación cromatográfica usando una columna quiral.

(c) Sales farmacéuticamente aceptables

[0223] A menos que se especifique lo contrario, la especificación de un compuesto en este documento incluye sales farmacéuticamente aceptables de tal compuesto. De esta manera, los compuestos descritos en este documento pueden estar en forma de sales farmacéuticamente aceptables, o pueden formularse como sales farmacéuticamente aceptables. Las formas contempladas de sal farmacéuticamente aceptable incluyen, sin limitación, mono, bis, tris, tetrakis, etcétera. Las sales farmacéuticamente aceptables no son tóxicas en las cantidades y concentraciones a las que se administran. La preparación de tales sales puede facilitar el uso farmacológico al alterar las características físicas de un compuesto sin evitar que ejerza su efecto fisiológico. Alteraciones útiles en propiedades físicas incluyen reducir el punto de fusión para facilitar la administración a través de mucosas e incrementar la solubilidad para facilitar administrar mayores concentraciones del fármaco. Un compuesto de la invención puede poseer un grupo suficientemente ácido, uno suficientemente básico, o ambos grupos funcionales, y por consiguiente puede reaccionar con cualquiera de una serie de bases inorgánicas u orgánicas, y ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable.

[0224] Sales farmacéuticamente aceptables incluyen sales de adición de ácido tales como aquellas que contienen cloruro, bromuro, yoduro, clorhidrato, acetato, fenilacetato, acrilato, ascorbato, aspartato, benzoato, 2-fenoxibenzoato, 2-acetoxibenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, metilbenzoato, bicarbonato, butino-1,4 dioato, hexino-1,6-dioato, caproato, caprilato, clorobenzoato, cinamato, citrato, decanoato, formato, fumarato, glicolato, gluconato, glucarato, glucuronato, glucosa-6-fosfato, glutamato, heptanoato, hexanoato, isetionato, isobutirato, gamma-hidroxibutirato, fenilbutirato, lactato, malato, maleato, hidroximaleato, metilmaleato, malonato, mandelato, nicotinato, nitrato, isonicotinato, octanoato, oleato, oxalato, pamoato, fosfato, monofosfato ácido, difosfato ácido, ortofosfato, metafosfato, pirofosfato, 2-fosfoglicerato, 3-fosfoglicerato, ftalato, propionato, fenilpropionato, propiolato, piruvato, quinato, salicilato, 4-aminosalicilato, sebacato,

estearato, suberato, succinato, sulfato, pirosulfato, bisulfato, sulfito, bisulfito, sulfamato, sulfonato, bencensulfonato (es decir, besilato), etanosulfonato (es decir, esilato), etano-1,2-disulfonato, 2-hidroxietanosulfonato (es decir, isetionato), metanosulfonato (es decir, mesilato), naftaleno-1-sulfonato, naftaleno-2-sulfonato (es decir, napsilato), propanosulfonato, *p*-toluensulfonato (es decir, tosilato), xilensulfonatos, ciclohexilsulfamato, tartrato, y trifluoroacetato. Estas sales farmacéuticamente aceptables de adición de ácido pueden prepararse usando el ácido correspondiente apropiado.

[0225] Cuando grupos funcionales ácido, tal como ácido carboxílico o fenol se presentan, las sales farmacéuticamente aceptables también incluyen sales de adición de base tales como aquellas que contienen benzatina, cloroprocaína, colina, etanolamina, dietanolamina, trietanolamina, t-butilamina, diciclohexilamina, etilenodiamina, N,N'-dibenciletilenodiamina, meglumina, hidroxietilpirrolidina, piperidina, morfolina, piperazina, procaína, aluminio, calcio, cobre, hierro, litio, magnesio, manganeso, potasio, sodio, zinc, amonio, y mono-, di-, o tri-alquilaminas (por ejemplo, dietilamina), o sales derivadas de aminoácidos tales como L-histidina, L-glicina, L-lisina, y L-arginina. Por ejemplo, véase *Remington's Pharmaceutical Sciences*, 19ª ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Estas sales farmacéuticamente aceptables de adición de base pueden prepararse usando la base correspondiente apropiada.

[0226] Las sales farmacéuticamente aceptables pueden prepararse por técnicas estándar. Por ejemplo, la forma de base libre de un compuesto puede disolverse en un solvente adecuado, tal como una solución acuosa o acuosa-alcohol que contiene el ácido apropiado y entonces aislarse al evaporar la solución. En otro ejemplo, una sal puede prepararse al hacer reaccionar la base y ácido libre en un solvente orgánico. Si el compuesto particular es un ácido, la sal deseada farmacéuticamente aceptable puede prepararse por cualquier método adecuado, por ejemplo, tratamiento del ácido libre con una base inorgánica u orgánica apropiada.

(d) Otras formas de compuestos

[0227] En el caso de agentes que son sólidos, se entiende por los expertos en la técnica que los compuestos y sales pueden existir en diferentes formas cristalinas o polimórficas, o pueden formularse como co-cristales, o pueden estar en forma amorfa, o pueden ser cualquier combinación de los mismos (por ejemplo, parcialmente cristalina, parcialmente amorfa, o mezclas de polimorfos) todas las cuales pretenden estar dentro del alcance de la presente invención y fórmulas especificadas. Mientras que las sales se forman por adición de ácido/base, es decir, una base libre o ácido libre del compuesto de interés forma una reacción ácido/base con una base de adición o ácido de adición correspondiente, respectivamente, que resulta en una interacción de carga iónica, los co-cristales son

una nueva especie química que se forma entre compuestos neutros, que resulta en el compuesto y una especie molecular adicional en la misma estructura cristalina.

[0228] En algunos casos, los compuestos de la invención forman complejos con un ácido o una base, incluyendo sales de adición de base tal como amonio, dietilamina, etanolamina, etilenodiamina, dietanolamina, t-butilamina, piperazina, meglumina; sales de adición de ácido, tal como acetato, acetilsalicilato, besilato, camsilato, citrato, formato, fumarato, glutarato, clorhidrato, maleato, mesilato, nitrato, oxalato, fosfato, succinato, sulfato, tartrato, tiocianato y tosilato; y aminoácidos tales como alanina, arginina, asparagina, ácido aspártico, cisteína, glutamina, ácido glutámico, glicina, histidina, isoleucina, leucina, lisina, metionina, fenilalanina, prolina, serina, treonina, triptofano, tirosina o valina. Al combinar el compuesto de la invención con el ácido o base, un complejo amorfo se forma preferiblemente en lugar de un material cristalino tal como una sal típica o co-cristal. En algunos casos, la forma amorfa del complejo se facilita por procesamiento adicional, tal como por secado por aspersión, métodos mecanoquímicos tal como compactación por rodillos, o irradiación de microondas del compuesto original mezclado con el ácido o base. Tales métodos también pueden incluir la adición de sistemas poliméricos iónicos y/o no iónicos, incluyendo, pero sin limitarse a, acetato succinato de hidroxipropil metil celulosa (HPMCAS) y copolímero de ácido metacrílico (por ejemplo, Eudragit® L100-55), que estabilizan además la naturaleza amorfa del complejo. Tales complejos amorfos proporcionan varias ventajas. Por ejemplo, la disminución de la temperatura de fusión en relación con la base libre facilita el procesamiento adicional, tal como extrusión de fundido en caliente, para mejorar además las propiedades biofarmacéuticas del compuesto. También, el complejo amorfo es fácilmente friable, lo que proporciona compresión mejorada para la carga del sólido en forma de cápsula o tableta.

[0229] Adicionalmente, las fórmulas pretenden cubrir formas hidratadas o solvatadas así como no hidratadas o no solvatadas de las estructuras identificadas. Por ejemplo, los compuestos indicados incluyen formas hidratadas y no hidratadas. Otros ejemplos de solvatos incluyen las estructuras en combinación con un solvente adecuado, tal como isopropanol, etanol, metanol, DMSO, etilacetato, ácido acético, o etanolamina.

Formulaciones y Administración

[0230] Los métodos y compuestos típicamente se usarán en terapia para sujetos humanos. Sin embargo, también pueden usarse para tratar indicaciones similares o idénticas en otros sujetos animales. Los compuestos descritos en este documento pueden administrarse por diferentes rutas, incluyendo inyección (es decir, parenteral, incluyendo intravenosa, intraperitoneal, subcutánea, e intramuscular), oral, transdérmica, a través de mucosas, rectal, o inhalante. Tales formas de dosificación deben permitir al compuesto alcanzar las células objetivo. Otros factores se conocen

bien en la técnica, e incluyen consideraciones tales como toxicidad y formas de dosificación que retardan al compuesto o composición para ejercer sus efectos. Técnicas y formulaciones generalmente pueden encontrarse en Remington: *The Science and Practice of Pharmacy*, 21ª edición, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (incorporada por la presente para referencia en este documento).

[0231] En algunas modalidades, las composiciones comprenderán portadores o excipientes farmacéuticamente aceptables, tal como rellenos, aglutinantes, desintegrantes, agentes de flujo, lubricantes, agentes de complejo, solubilizantes, y tensoactivos, que pueden elegirse para facilitar la administración del compuesto por una ruta particular. Ejemplos de portadores incluyen carbonato de calcio, fosfato de calcio, diversos azúcares tales como lactosa, glucosa, o sacarosa, tipos de almidón, derivados de celulosa, gelatina, lípidos, liposomas, nanopartículas, y similares. Los portadores también incluyen líquidos fisiológicamente compatibles como solventes o para suspensiones, incluyendo, por ejemplo, soluciones estériles de agua para inyección (WFI), solución salina, solución de dextrosa, solución de Hank, solución de Ringer, aceites vegetales, aceites minerales, aceites animales, polietilenglicoles, parafina líquida, y similares. Los excipientes también pueden incluir, por ejemplo, dióxido de silicio coloidal, gel de sílice, talco, silicato de magnesio, silicato de calcio, aluminosilicato de sodio, trisilicato de magnesio, celulosa pulverizada, celulosa macrocristalina, carboximetilcelulosa, carboximetilcelulosa sódica reticulada, benzoato de sodio, carbonato de calcio, carbonato de magnesio, ácido esteárico, estearato de aluminio, estearato de calcio, estearato de magnesio, estearato de zinc, estearilfumarato de sodio, siloide, estearowet C, óxido de magnesio, almidón, glicolato de almidón sódico, monoestearato de glicerilo, dibehenato de glicerilo, palmitoestearato de glicerilo, aceite vegetal hidrogenado, aceite hidrogenado de semilla de algodón, aceite mineral de aceite de semillas de ricino, polietilenglicol (por ejemplo, PEG 4000-8000), polioxietilenglicol, poloxámeros, povidona, crospovidona, croscarmelosa sódica, ácido algínico, caseína, copolímero ácido metacrílico divinilbenceno, docusato de sodio, ciclodextrinas (por ejemplo, 2-hidroxipropil-.delta.-ciclodextrina), polisorbatos (por ejemplo, polisorbato 80), cetrimida, TPGS (d-alfa-tocoferilo polietilenglicol 1000 succinato), laurilsulfato de magnesio, laurilsulfato de sodio, polietilenglicoléteres, di-éster de ácidos grasos de polietilenglicoles, o un éster de polioxialquilensorbitan de ácidos grasos (por ejemplo, polioxietilensorbitanéster Tween®), polioxietilensorbitanésteres de ácidos grasos, sorbitanéster de ácidos grasos, por ejemplo, un sorbitanéster de ácidos grasos de un ácido graso tal como ácido oleico, esteárico o palmítico, manitol, xilitol, sorbitol, maltosa, lactosa, lactosa monohidratada o lactosa seca por aspersión, sacarosa, fructosa, fosfato de calcio, fosfato de calcio dibásico, fosfato de calcio tribásico, sulfato de calcio, dextratos, dextrano, dextrina, dextrosa, acetato de celulosa, maltodextrina, simeticona, polidextrosam, quitosana, gelatina, HPMC (hidroxipropilmetilcelulosas), HPC (hidroxipropilcelulosa), hidroxietilcelulosa, y similares.

[0232] En algunas modalidades, puede usarse administración oral. Las preparaciones farmacéuticas para su uso oral pueden formularse en formas convencionales orales de dosificación tales como cápsulas, tabletas, y preparaciones líquidas tales como jarabes, elíxires, y gotas concentradas. Los compuestos descritos en este documento pueden combinarse con excipientes sólidos, moliendo opcionalmente una mezcla resultante, y procesando la mezcla de gránulos, después de agregar auxiliares adecuados, si se desea, para obtener, por ejemplo, tabletas, tabletas recubiertas, cápsulas duras, cápsulas suaves, soluciones (por ejemplo, soluciones acuosas, alcohólicas, u oleosas) y similares. Los excipientes adecuados son, en particular, rellenos tales como azúcares, incluyendo lactosa, glucosa, sacarosa, manitol, o sorbitol; preparaciones de celulosa, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de papa, gelatina, goma tragacanto, metilcelulosa, hidroxipropilmetil-celulosa, carboximetilcelulosa sódica (CMC), y/o polivinilpirrolidona (PVP: povidona); excipientes oleosos, incluyendo aceites vegetales y animales, tales como aceite de girasol, aceite de oliva, o aceite de hígado de bacalao. Las formulaciones de dosificación oral también pueden contener agentes desintegrantes, tal como la polivinilpirrolidona reticulada, agar, o ácido algínico, o una sal de los mismos tal como alginato de sodio; un lubricante, tal como talco o estearato de magnesio; un plastificante, tal como glicerol o sorbitol; un edulcorante tal como sacarosa, fructosa, lactosa, o aspartame; un agente saborizante natural o artificial, tal como menta piperina, aceite de hierbabuena, o saborizante de cereza; o colorantes o pigmentos, que pueden usarse para la identificación o caracterización de diferentes dosis o combinaciones. También se proporcionan centros de grageas con recubrimientos adecuados. Para este propósito, pueden usarse soluciones concentradas de azúcar, que pueden contener opcionalmente, por ejemplo, goma arábiga, talco, polivinilpirrolidona, gel carbopol, polietilenglicol, y/o dióxido de titanio, soluciones de laca, y solventes o mezclas de solventes orgánicos adecuados.

[0233] Las preparaciones farmacéuticas que pueden usarse en forma oral incluyen cápsulas rígidas hechas de gelatina ("gelcaps"), así como cápsulas suaves selladas hechas de gelatina, y un plastificante, tal como glicerol o sorbitol. Las cápsulas rígidas pueden contener los ingredientes activos en mezcla con un relleno tal como lactosa, aglutinantes tales como almidones, y/o lubricantes tales como talco o estearato de magnesio y, opcionalmente, estabilizantes. En las cápsulas suaves, los compuestos activos pueden disolverse o suspenderse en líquidos adecuados, tales como aceites grasos, parafina líquida, o polietilenglicoles líquidos.

[0234] En algunas modalidades, puede usarse inyección (administración parenteral), *por ejemplo*, intramuscular, intravenosa, intraperitoneal, y/o subcutánea. Los compuestos descritos en este documento para inyección pueden formularse en soluciones líquidas estériles, preferiblemente en reguladores o soluciones fisiológicamente compatibles, tales como solución salina, solución de Hank, o solución de Ringer. También pueden prepararse dispersiones en soluciones no acuosas, tales como

glicerol, propilenglicol, etanol, polietilenglicoles líquidos, triacetina, y aceites vegetales. Las soluciones también pueden contener un conservador, tal como metilparabeno, propilparabeno, clorobutanol, fenol, ácido sórbico, timerosal, y similares. Además, los compuestos pueden formularse en forma sólida, incluyendo, por ejemplo, formas liofilizadas, y redisolverse o suspenderse antes de su uso.

[0235] En algunas modalidades, puede usarse administración a través de mucosas, tópica o transdérmica. En tales formulaciones de los compuestos descritos en este documento, se usan penetrantes apropiados para la barrera que se traspasará. Tales penetrantes generalmente se conocen en la técnica, e incluyen, por ejemplo, para administración a través de mucosas, sales biliares y derivados de ácido fusídico. Además, pueden usarse detergentes para facilitar la permeación. La administración a través de mucosas, por ejemplo, puede ser a través de aspersiones nasales o supositorios (rectal o vaginal). Las composiciones de los compuestos descritos en este documento para administración tópica pueden formularse como aceites, cremas, lociones, ungüentos, y similares por la elección de portadores apropiados conocidos en la técnica. Los portadores adecuados incluyen aceites vegetales o minerales, vaselina (parafina blanca suave), grasas o aceites de cadena ramificada, grasas animales y alcohol de alto peso molecular (más de C_{12}). En algunas modalidades, se seleccionan portadores de tal modo que el ingrediente activo sea soluble. Emulsionantes, estabilizantes, humectantes y antioxidantes también pueden incluirse, así como agentes que imparten color o fragancia, si se desea. Las cremas para aplicación tópica se formulan preferiblemente a partir de una mezcla de aceite mineral, cera de abeja auto-emulsionante y agua en cuya mezcla el ingrediente activo, disuelto en una pequeña cantidad de solvente (por ejemplo, un aceite), se mezcla. Adicionalmente, la administración por medios transdérmicos puede comprender un parche o apósito transdérmico tal como un vendaje impregnado con un ingrediente activo y opcionalmente uno o más portadores o diluyentes conocidos en la técnica. Para administrarse en forma de un sistema de suministro transdérmico, la administración de la dosificación será continua en lugar de intermitente a lo largo del régimen de dosificación.

[0236] En algunas modalidades, los compuestos se administran como inhalantes. Los compuestos descritos en este documento pueden formularse como polvo seco o una solución, suspensión, o aerosol adecuado. Los polvos y soluciones pueden formularse con aditivos adecuados conocidos en la técnica. Por ejemplo, los polvos pueden incluir una base adecuada de polvo tal como lactosa o almidón, y las soluciones pueden comprender propilenglicol, agua estéril, etanol, cloruro de sodio y otros aditivos, tales como ácido, álcali y sales reguladoras. Tales soluciones o suspensiones pueden administrarse al inhalar mediante aspersión, bomba, atomizador, o nebulizador, y similares. Los compuestos descritos en este documento también pueden usarse en combinación con otras terapias inhaladas, por ejemplo corticosteroides tales como propionato de fluticasona, dipropionato de

beclometasona, triamcinolona acetonida, budesonida, y furoato de mometasona; beta agonistas tales como albuterol, salmeterol, y formoterol; agentes anticolinérgicos tales como bromuro de ipratroprio o tiotropio; vasodilatadores tales como treprostinal e iloprost; enzimas tales como DNAasa; proteínas terapéuticas; anticuerpos de inmunoglobulina; un oligonucleótido, tal como DNA o RNA de una sola o doble hebra, siRNA; antibióticos tales como tobramicina; antagonistas de receptores muscarínicos; antagonistas de leucotrienos; antagonistas de citocinas; inhibidores de proteasas; cromolin sódico; nedocril sódico; y cromoglicato de sodio.

[0237] Las cantidades de diversos compuestos para administrarse pueden determinarse por procedimientos estándar tomando en cuenta factores tales como la actividad del compuesto (*in vitro*, por ejemplo, la IC_{50} del compuesto vs. objetivo, o actividad *in vivo* en modelos animales de eficacia), resultados de farmacocinética en modelos animales (por ejemplo, vida media biológica o biodisponibilidad), la edad, tamaño, y peso del sujeto, y el trastorno asociado con el sujeto. La importancia de estos y otros factores se conoce bien por los expertos en la técnica. Generalmente, una dosis será en el intervalo de alrededor de 0.01 a 50 mg/kg, también alrededor de 0.1 a 20 mg/kg del sujeto que se trata. Múltiples dosis pueden usarse.

[0238] Los compuestos descritos en este documento también pueden usarse en combinación con otras terapias para tratar la misma enfermedad. Tal uso de combinación incluye la administración de los compuestos y uno o más terapéuticos diferentes en momentos diferentes, o co-administración del compuesto y una o más terapias diferentes. En algunas modalidades, la dosificación puede modificarse para uno o más de los compuestos de la invención u otros terapéuticos usados en combinación, por ejemplo, reducción en la cantidad dosificada en relación con un compuesto o terapia usada sola, por métodos bien conocidos por los expertos en la técnica.

[0239] Se entenderá que el uso en combinación incluye el uso con otras terapias, fármacos, procedimientos médicos, etc., en donde la otra terapia o procedimiento puede administrarse en períodos diferentes (por ejemplo, dentro de un tiempo corto, tal como en el lapso de horas (por ejemplo, 1, 2, 3, 4-24 horas), o dentro de un tiempo prolongado (por ejemplo, 1-2 días, 2-4 días, 4-7 días, 1-4 semanas)) a los de un compuesto descrito en este documento, o al mismo tiempo que un compuesto descrito en este documento. El uso en combinación también incluye el uso con una terapia o procedimiento médico que se administra una vez u ocasionalmente, tal como cirugía, junto con un compuesto descrito en este documento administrado dentro de un período corto o período prolongado, antes o después de la otra terapia o procedimiento. En algunas modalidades, la presente invención permite el suministro de un compuesto descrito en este documento y uno o más terapéuticos farmacológicos diferentes suministrados por una ruta diferente de administración o por la misma ruta de administración. El uso en combinación para cualquier ruta de administración incluye el suministro de un compuesto descrito en este documento y uno o más terapéuticos farmacológicos diferentes

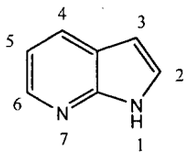
suministrados por la misma ruta de administración en conjunto en cualquier formulación, incluyendo formulaciones donde los dos compuestos se enlazan químicamente en tal forma que mantienen su actividad terapéutica cuando se administraron. En un aspecto, la otra terapia farmacológica puede co-administrarse con un compuesto descrito en este documento. El uso en combinación por la co-administración incluye la administración de co-formulaciones o formulaciones de compuestos unidos químicamente, o la administración de dos o más compuestos en formulaciones separadas dentro de un período corto de tiempo entre sí (por ejemplo, en el lapso de 2 horas, 3 horas, hasta 24 horas), administrados por la misma o diferentes rutas. La co-administración de formulaciones separadas incluye co-administración por suministro mediante un dispositivo, por ejemplo el mismo dispositivo inhalante, la misma jeringa, etc., o la administración desde dispositivos separados dentro de un tiempo corto entre sí. Las co-formulaciones de un compuesto descrito en este documento y una o más farmacoterapias adicionales suministradas por la misma ruta incluyen preparación de los materiales en conjunto de tal modo que puedan administrarse por un dispositivo, incluyendo los compuestos separados combinados en una formulación, o compuestos que se modifican de tal modo que se asocian químicamente, y todavía mantienen aún su actividad biológica. Tales compuestos químicamente asociados pueden tener un enlace que se mantiene sustancialmente *in vivo*, o el enlace puede deteriorarse *in vivo*, separando los dos componentes activos.

EJEMPLOS

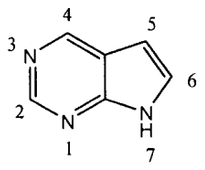
[0240] Ejemplos relacionados con la presente invención se describen a continuación. En la mayor parte de los casos, pueden usarse técnicas alternativas. Los ejemplos pretenden ser ilustrativos y no son limitantes o restrictivos para el alcance de la invención. En algunos ejemplos, el resultado de la espectrometría de masas indicado para un compuesto puede tener más de un valor debido a la distribución de isótopos de un átomo en la molécula, tal como un compuesto que tiene un sustituyente bromo o cloro. Los compuestos en los siguientes ejemplos se caracterizan por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

[0241] A menos que se indique específicamente de otra manera, la enumeración de la Fórmula y enumeración de grupos R usados en los siguientes ejemplos no se relaciona con tal enumeración en otras secciones de esta solicitud. Los reactivos y solventes usados en estos ejemplos pueden sustituirse fácilmente con alternativas apropiadas como se conocen en la técnica y el aislamiento de los productos se alcanza fácilmente por métodos conocidos en la técnica, incluyendo, pero sin limitarse a, extracción, cristalización, y métodos cromatográficos.

[0242] La numeración del anillo para la 1H-pirrolo[2,3-b]piridina en los siguientes Ejemplos es como sigue:



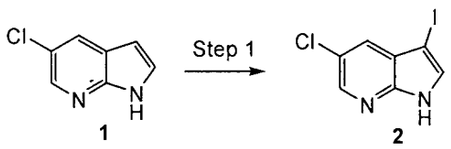
[0243] La numeración del anillo para la 7H-pirrolo[2,3-d]pirimidina en los siguientes Ejemplos es como sigue:



Ejemplo 1: Síntesis de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina 2.

[0244] 5-Cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** se preparó en una etapa a partir de 5-cloro-1H-pirrolo[2,3-b]piridina **1** como se muestra en el Esquema 1.

Esquema 1



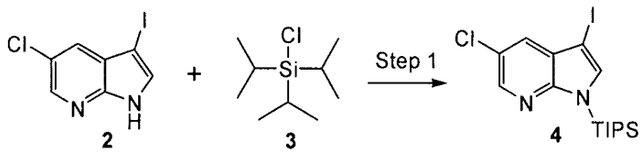
Etapa 1 – Preparación de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (2):

[0245] 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 nitrógeno, piridina (7.951 ml, 98.31 mmol) y monocloruro de yodo (110 ml, 1.0 M en diclorometano, 110 mmol) se agregaron lentamente durante 20 minutos. La reacción se agitó a temperatura ambiente durante 2 horas, luego se extinguió con 100 ml de pentahidrato de tiosulfato de sodio acuoso 1 M. Las capas se separaron, los sólidos se recolectaron de la capa acuosa por filtración y se combinaron con la capa orgánica. La capa acuosa se extrajo con acetato de etilo, las capas orgánicas se combinaron y lavaron con salmuera, luego se concentraron bajo vacío. El sólido resultante se lavó con acetato de etilo al 20% en hexano para proporcionar el compuesto deseado. 5-fluoro-3-yodo-1H-pirrolo[2,3-b]piridina se prepara de manera similar a partir de 5-fluoro-1H-pirrolo[2,3-b]piridina.

Ejemplo 2: Síntesis de 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina 4.

[0246] 5-Cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **4** se preparó en una etapa a partir de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** como se muestra en el Esquema 2.

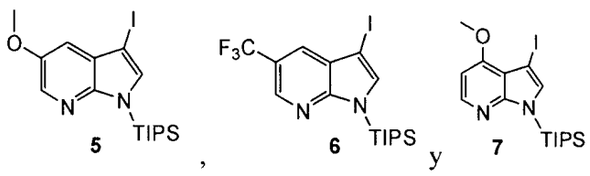
Esquema 2



Etapa 1 – Preparación de 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (4):

[0247] A 5-cloro-3-iodo-1H-pirrolo[2,3-b]piridina (**2**, 16.50 g, 59.25 mmol) en 250.0 ml de N,N-dimetilformamida, se agregó hidruro de sodio (3.10 g, 60% en aceite mineral, 77.5 mmol). La reacción se agitó a temperatura ambiente durante 90 minutos, entonces se agregó lentamente cloruro de triisopropisililo (**3**, 13.00 ml, 61.36 mmol). La reacción se agitó a temperatura ambiente durante la noche, entonces se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**4**, 10.0 g). 5-fluoro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina se prepara de manera similar a partir de 5-fluoro-3-yodo-1H-pirrolo[2,3-b]piridina.

[0248] 3-Yodo-5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **5**, 3-yodo-5-trifluorometil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **6**, y 3-yodo-4-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina 7

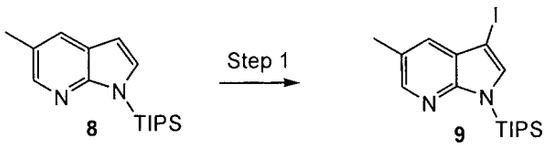


se preparan de manera similar al protocolo del Esquema 2, reemplazando 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** con 3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina, 3-yodo-5-trifluorometil-1H-pirrolo[2,3-b]piridina, y 3-yodo-4-metoxi-1H-pirrolo[2,3-b]piridina, respectivamente. MS (ESI) $[M+H^+]^+$ = 431.2 (compuesto **5**) y 469.4 (compuesto **6**).

Ejemplo 3: Síntesis de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina 9.

[0249] 3-Yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **9** se preparó en una etapa a partir de 5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** como se muestra en el Esquema 3.

Esquema 3



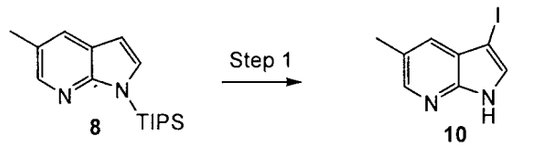
*Etapa 1 – Preparación de 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**9**):*

[0250] 5-Metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**, 1.1 g, 3.8 mmol) y 10 ml de diclorometano se combinaron en un matraz de fondo redondo y se agitaron durante 10 minutos. Una suspensión de N-yodosuccinimida (1.0 g, 4.6 mmol) en 5 ml de diclorometano se agregó y agitó a temperatura ambiente durante la noche. La reacción se extinguió con tiosulfato de sodio (20 ml, 1M en agua) y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con agua y salmuera, se secó con sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con etilacetato y hexanos. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un aceite amarilo claro (**9**, 1.2 g, 75%). MS (ESI) $[M+H^+]^+ = 415.08$.

Ejemplo 4: Síntesis de 3-yodo-5-metil-1H-pirrolo[2,3-b]piridina 10.

[0251] 3-Yodo-5-metil-1H-pirrolo[2,3-b]piridina **10** se preparó en una etapa a partir de 5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **8** como se muestra en el Esquema 4.

Esquema 4



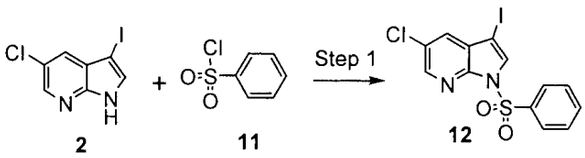
*Etapa 1 – Preparación de 3-yodo-5-metil-1H-pirrolo[2,3-b]piridina (**10**):*

[0252] A una solución de 5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**8**, 1 g, 2.0 mmol) en 10 ml de tetrahidrofurano, yodo (0.43 g, 1.7 mmol) en 5 ml de tetrahidrofurano se agregó. La reacción se agitó a temperatura ambiente durante la noche, luego se extinguió con 20 ml de 1M tiosulfato de sodio acuoso y se extrajo con acetato de etilo. Las capas orgánicas se combinaron y lavaron con agua, salmuera, se secaron sobre sulfato de sodio, se filtraron y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo y hexanos. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**10**, 20 mg). MS (ESI) $[M+H^+]^+ = 258.70$.

Ejemplo 5: Síntesis de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina 12.

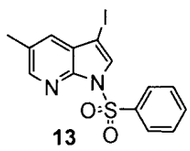
[0253] 1-Bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **12** se preparó en 1 etapa a partir de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** y cloruro de bencenosulfonilo **11** como se muestra en el Esquema 5.

Esquema 5



Etapa 1 – Preparación de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (12):

[0254] A una solución de 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**2**, 5.00 g, 18.0 mmol) en 80.0 ml de N,N-dimetilformamida, hidruro de sodio (1.1 g, 60% en aceite mineral, 27.0 mmol) se agregó lentamente. Una solución de cloruro de bencenosulfonilo (**11**, 2.40 ml, 18.8 mmol) en 10.0 ml de N,N-dimetilformamida se agregó por goteo a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 15 horas, luego se vertió en agua helada y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El sólido resultante se lavó con 5% de acetato de etilo en hexano, se aisló por filtración, y se secó para proporcionar el compuesto deseado (**12**, 5.9 g). ^{1}H NMR fue consistente con la estructura del compuesto. 1-Bencenosulfonil-3-yodo-5-metil-1H-pirrolo[2,3-b]piridina **13**

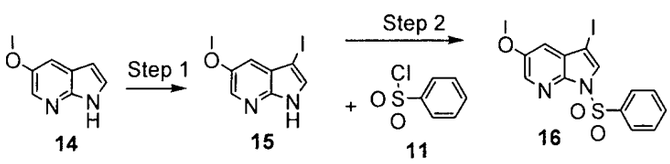


se preparó de manera similar a este protocolo, reemplazando 5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **2** con 3-yodo-5-metil-1H-pirrolo[2,3-b]piridina **10**. 1-Bencenosulfonil-5-fluoro-3-yodo-1H-pirrolo[2,3-b]piridina se prepara de manera similar a partir de 5-fluoro-3-yodo-1H-pirrolo[2,3-b]piridina.

Ejemplo 6: Síntesis de 1-bencenosulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina 16.

[0255] 1-Bencenosulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina **16** se preparó en dos etapas a partir de 5-metoxi-1H-pirrolo[2,3-b]piridina **14** como se muestra en el Esquema 6.

Esquema 6



*Etapa 1 – Preparación de 3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina (**15**):*

[0256] A una solución de 5-metoxi-1H-pirrolo[2,3-b]piridina (**14**, 300 mg, 2.0 mmol) en 30 ml de diclorometano bajo nitrógeno, monocloruro de yodo (3 ml, 1.0 M en diclorometano, 3.0 mmol) se agregó a -40 °C. La reacción se agitó a temperatura ambiente, luego se extinguió con 10 ml de 1 M tiosulfato de sodio acuoso pentahidratado. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron y lavaron con agua, salmuera, luego se secaron sobre sulfato de sodio, se decoloraron con carbón activado, se filtraron y el filtrado se concentró bajo vacío. El sólido resultante se lavó con 20% de acetato de etilo en hexano para proporcionar el compuesto deseado (**15**, 371 mg). MS (ESI) $[M+H^+]^+ = 275.03$.

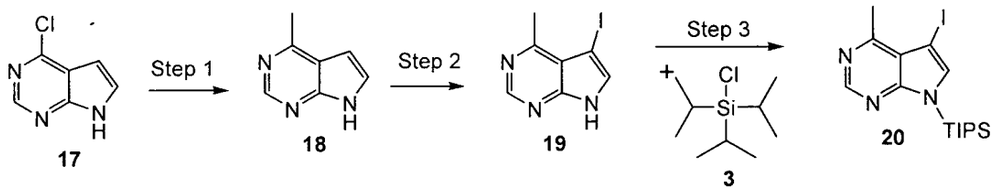
*Etapa 2 – Preparación de 1-bencenosulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina (**16**):*

[0257] A una solución de 3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina (**15**, 4.30 g, 15.7 mmol) en 53.6 ml de N,N-dimetilformamida bajo nitrógeno, hidruro de sodio (0.690 g, 60% en aceite mineral, 17.2 mmol) se agregó. Después de 10 minutos, cloruro de bencenosulfonilo (**11**, 2.20 ml, 17.2 mmol) se agregó y la reacción se enfrió en un baño maría. La reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se purificó por cromatografía de columna en gel de sílice, eluyendo con 30-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**16**, 4.60 g).

Ejemplo 7: Síntesis de 5-yodo-4-metil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina 20.

[0258] 5-Yodo-4-metil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina **20** se preparó en dos etapas a partir de 4-cloro-7H-pirrolo[2,3-d]pirimidina **17** como se muestra en el Esquema 7.

Esquema 7



*Etapa 1 – Preparación de 4-metil-7H-pirrolo[2,3-d]pirimidina (**18**):*

[0259] A 4-cloro-7H-pirrolo[2,3-d]pirimidina (**17**, 5.03 g, 32.8 mmol) en 100 ml de tolueno, [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II) 1:1 complejo con diclorometano (0.627 g, 0.328 mmol) se agregó bajo nitrógeno. Después de agitar durante 10 minutos, bromuro de metilmagnesio (62.9 ml, 3.00 M en éter, 189 mmol) se agregó lentamente. La reacción se calentó a 55 °C durante la noche, luego se enfrió a -70 a -80 °C y se extinguió al agregar cloruro de amonio por goteo. Luego 1N ácido clorhídrico se agregó y el pH se ajustó a 7-8 con adición de bicarbonato de sodio saturado. Este se extrajo 3x con acetato de etilo. La capa orgánica combinada se lavó con cloruro de amonio saturado y

salmuera, luego se secó con sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo y diclorometano, luego metanol y diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido marrón (**18**). MS (ESI) $[M+H^+]^+ = 134$.

*Etapa 2 – Preparación de 5-yodo-4-metil-7H-pirrolo[2,3-d]pirimidina (**19**):*

[0260] A 4-metil-7H-pirrolo[2,3-d]pirimidina (**18**, 0.634 g, 4.76 mmol) en 50 ml de diclorometano, N-yodosuccinimida (1.3 g, 5.7 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 45 minutos. La reacción se concentró bajo vacío, luego acetato de etilo se agregó y se lavó con 1 N tiosulfato de sodio acuoso. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**19**, 0.94 g). MS (ESI) $[M+H^+]^+ = 260.26$.

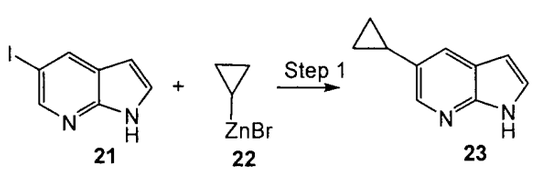
*Etapa 3 – Preparación de 5-yodo-4-metil-7-triisopropilsilanil-7H-pirrolo[2,3-d]pirimidina (**20**):*

[0261] A 5-yodo-4-metil-7H-pirrolo[2,3-d]pirimidina (**19**, 323.6 mg, 1.25 mmol) en 8 ml de tetrahidrofurano bajo nitrógeno, hidruro de sodio (57.41 mg, 60% en aceite mineral, 1.44 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 10 minutos, luego cloruro de triisopropilsililo (**3**, 0.304 ml, 1.44 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 2 horas, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado.

Ejemplo 8: Síntesis de 5-ciclopropil-1H-pirrolo[2,3-b]piridina 23.

[0262] 5-Ciclopropil-1H-pirrolo[2,3-b]piridina **23** se preparó en una etapa a partir de 5-yodo-1H-pirrolo[2,3-b]piridina **21** como se muestra en el Esquema 8.

Esquema 8



*Etapa 1– Preparación de 5-ciclopropil-1H-pirrolo[2,3-b]piridina (**23**):*

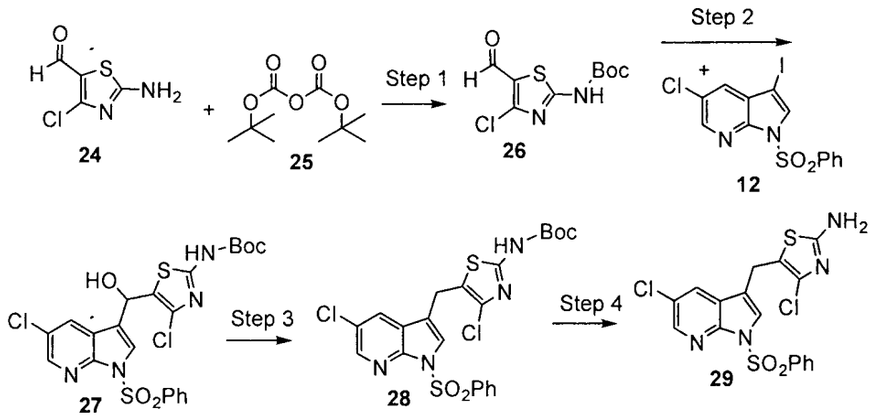
[0263] 5-Yodo-1H-pirrolo[2,3-b]piridina (**21**, 0.343 g, 1.40 mmol), bromuro de ciclopropilzinc (**22**, 12.6 ml, 0.500 M en tetrahidrofurano, 6.32 mmol) y cloruro de [1,3-bis(difenilfosfino)propano]-níquel(II) (76.2 mg, 0.14 mmol) y 5.37 ml de 1,4-dioxano se combinaron en un recipiente de reacción.

La reacción se calentó a 100 °C durante la noche, luego se agregó metanol y la reacción se concentró bajo vacío. Acetato de etilo y agua se agregaron al residuo, luego se filtró a través de una almohadilla de celite y la almohadilla de celite se lavó con acetato de etilo. El filtrado se separó y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron y lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 159.0$.

Ejemplo 9: Síntesis de intermediario 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina 29

[0264] 5-(1-Bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **29** se sintetizó en 4 etapas a partir de 2-amino-4-cloro-tiazol-5-carbaldehído **24** como se muestra en el Esquema 9.

Esquema 9



*Etapa 1 – Síntesis de ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**26**):*

[0265] A 2-amino-4-cloro-tiazol-5-carbaldehído (**24**, 5.00 g, 0.0308 mol) en 122 ml de tetrahidrofurano, di-ter-butildicarbonato (**25**, 7.38 g, 0.0338 mol) y 4-dimetilaminopiridina (0.35 g, 0.0029 mol) se agregaron. La reacción se agitó a 58 °C durante 2 horas, luego se concentró bajo vacío y se purificó con cromatografía de columna en gel de sílice eluyendo con 20-80% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**26**, 7.0 g, 87%).

*Etapa 2 – Síntesis de ter-butiléster del ácido 5-[(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-4-cloro-tiazol-2-il-carbámico (**27**):*

[0266] A una solución de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**12**, 4.40 g,

10.5 mmol) en 30.0 ml de tetrahidrofurano a -45 °C bajo nitrógeno, una solución de cloruro de isopropilmagnesio (5.4 ml, 2.0 M en tetrahidrofurano) se agregó lentamente durante 10 minutos. La reacción se dejó calentar a -25 °C durante 30 minutos, luego se enfrió a -65 °C, seguido la adición del ter-butiléster frío y desprotonado del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico, el cual se preparó *in situ* al agregar cloruro de isopropilmagnesio (5.0 ml, 2.0 M en tetrahidrofurano) a ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**26**, 2.51 g, 9.55 mmol) en 23.0 ml de tetrahidrofurano a -78 °C bajo nitrógeno. La reacción se dejó calentar a temperatura ambiente durante 2 horas, luego se vertió en cloruro de amonio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró, y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 25-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**27**, 3.70 g, 60.3%). MS (ESI) $[M+H^+]^+ = 554.2$.

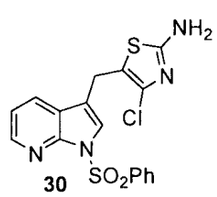
*Etapa 3 – Síntesis de ter-butiléster del ácido [5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-carbámico (**28**):*

[0267] A ter-butiléster del ácido 5-[(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-4-cloro-tiazol-2-il-carbámico (**27**, 0.200 g, 0.32 mmol) en 15.0 ml de diclorometano, trietilsilano (0.600 ml, 376 mmol) y ácido trifluoroacético (0.300 ml, 3.89 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 3 horas, luego se concentró, se vertió en carbonato de potasio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró, y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 25-100% de acetato de etilo en hexano para dar el compuesto deseado (**28**, 0.155 g, 88.7%). MS (ESI) $[M+H^+]^+ = 538.9$.

*Etapa 4 – Síntesis de 5-(1-Bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina (**29**):*

[0268] A ter-butiléster del ácido [5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-carbámico (**28**, 4.30 g, 7.97 mmol) en 70.0 ml de diclorometano, una solución de cloruro de hidrógeno (42.0 ml, 4.00 M en 1,4-dioxano) se agregó. La reacción se agitó a temperatura ambiente durante 2 días, luego se concentró, y trituró con etil éter y acetato de etilo para proporcionar el compuesto deseado (**29**, 2.60 g, 74.2%). MS (ESI) $[M+H^+]^+ = 439.0$.

[0269] 5-(1-Bencenosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **30**



30

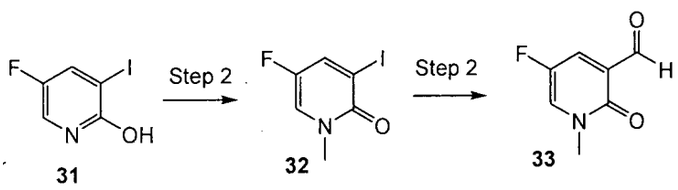
se preparó siguiendo el protocolo del Esquema 9, sustituyendo 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **12** con 1-bencenosulfonil-3-yodo-1H-pirrolo[2,3-b]piridina en la Etapa 2. MS (ESI) $[M+H^+]^+ = 404.4$.

Ejemplo 10: Síntesis de reactivos aldehído.

[0270] **Los r**eactivos aldehído que se usan para elaborar compuestos se preparan de acuerdo con los siguientes protocolos.

[0271] 5-Fluoro-1-metil-2-oxo-1,2-dihidro-piridin-3-carbaldehído **33** se preparó en dos etapas a partir de 5-fluoro-3-yodo-piridin-2-ol **31** como se muestra en el Esquema 10a.

Esquema 10a



Etapa 1 – Preparación de 5-fluoro-3-yodo-1-metil-1H-piridin-2-ona (32):

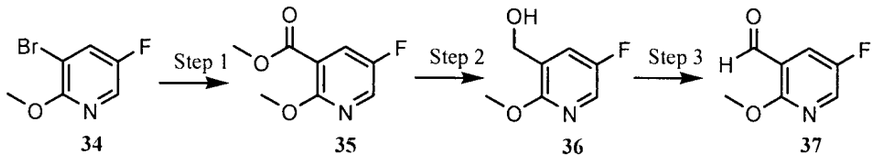
[0272] A 5-fluoro-3-yodo-piridin-2-ol (**31**, 200 g, 838 mmol) en 3000 ml de acetona se enfrió en un baño de agua helada. Carbonato de cesio (354 g, 1088 mmol) se agregó, luego yodometano (58.1 ml, 929 mmol) se agregó por goteo durante 30 minutos. La reacción se agitó durante la noche a temperatura ambiente. La reacción se concentró bajo vacío y el material resultante se dividió entre acetato de etilo y agua. La capa acuosa se aisló y ajustó a pH 3-4 con 3 N ácido clorhídrico, luego se extrajo con acetato de etilo. Las capas orgánicas combinadas se concentraron bajo vacío para proporcionar el compuesto deseado como un sólido blanquecino. (**32**, 150 g, 593 mmol, 70.8%).

Etapa 2 – Preparación de 5-fluoro-1-metil-2-oxo-1,2-dihidro-piridin-3-carbaldehído (33):

[0273] 5-Fluoro-3-yodo-1-metil-1H-piridin-2-ona (**32**, 120.5 g, 476 mmol) se disolvió en 2381 ml de tetrahidrofurano y se enfrió a -40 °C en un baño de hielo seco y acetona. Cloruro de isopropilmagnesio (310 ml, 619 mmol) se agregó por goteo y la mezcla se agitó durante 30 minutos. Luego 92 ml de N,N-dimetilformamida se agregaron y la mezcla se dejó calentar a temperatura ambiente y se agitó durante la noche. La reacción se extinguió al agregar 200 ml de 10% de ácido clorhídrico acuoso, luego se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 100% de acetato de etilo. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**33**, 35 g, 226 mmol, 47.4%).

[0274] 5-Fluoro-2-metoxi-piridin-3-carbaldehído **37** se preparó en tres etapas a partir de 3-bromo-5-fluoro-2-metoxi-piridina **34** como se muestra en el Esquema 10b.

Esquema 10b



Etapa 1 – Preparación de metiléster del ácido 5-fluoro-2-metoxi-nicotínico (35):

[0275] En un bomba calorimétrica Parr de 2 L, 3-bromo-5-fluoro-2-metoxi-piridina (**34**, 14 g, 68.0 mmol), trietilamina (19.10 ml, 136 mmol) y [1,1'-bis(difenilfosfino)ferroceno]-dicloropaladio(II) (1.443 g, 1.767 mmol) se combinaron con 300 ml de metanol y se calentaron a 100 °C bajo 100 psi de monóxido de carbono durante la noche. La reacción se concentró bajo vacío, el residuo se disolvió en diclorometano, y se pasó a través de un tapón de sílice, eluyendo con acetato de etilo para proporcionar el compuesto deseado como un sólido blanco (**35**, 10 g, 54.0 mmol, 79%).

Etapa 2 – Preparación de (5-fluoro-2-metoxi-piridin-3-il)-metanol (36):

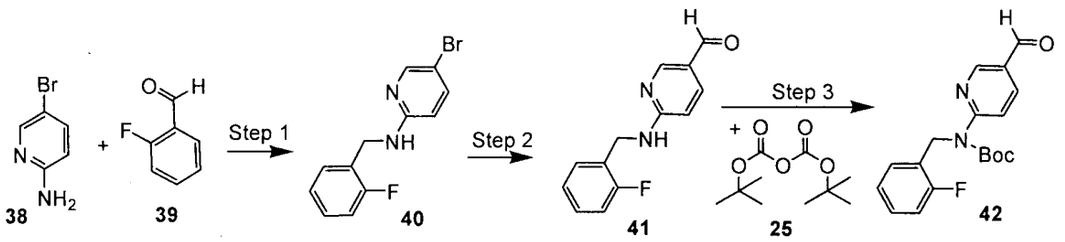
[0276] A metiléster del ácido 5-fluoro-2-metoxi-nicotínico (**35**, 10 g, 54.0 mmol) en 200 ml de tetrahidrofurano, hidruro de litio y aluminio (81 ml, 1 M en tetrahidrofurano, 81 mmol) se agregó por goteo a -78 °C y se agitó durante varias horas. La reacción se extinguió con adición por goteo de 3 ml de agua, 3 ml de 15% de hidróxido de sodio acuoso, y 10 ml de agua en secuencia, luego 200 ml de metil t-butil éter se agregaron. Los sólidos se filtraron y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**36**, 8 g, 50.9 mmol, 94%).

Etapa 3 – Preparación de 5-fluoro-2-metoxi-piridin-3-carbaldehído (37):

[0277] A (5-fluoro-2-metoxi-piridin-3-il)-metanol (**36**, 8 g, 50.9 mmol) en 300 ml de acetato de etilo, óxido de manganeso(IV) (39.8 g, 458 mmol) se agregó y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, y la almohadilla de celite se enjuagó con acetato de etilo. El filtrado se concentró bajo vacío, luego se pasó a través de un tapón de sílice, eluyendo con 50% de acetato de etilo en heptano para proporcionar el compuesto deseado como un sólido amarillo claro (**37**, 4.5 g, 29.0 mmol, 57.0% de rendimiento).

[0278] ter-butiléster del ácido (2-Fluoro-bencil)-(5-formil-piridin-2-il)-carbámico **42** se preparó en tres etapas a partir de 5-bromo-piridin-2-ilamina **38** y 2-fluoro-benzaldehído **39** como se muestra en el Esquema 10c.

Esquema 10c



*Etapa 1 – Preparación de (5-bromo-piridin-2-il)-(2-fluoro-bencil)-amina (**40**):*

[0279] En un matraz de fondo redondo, 5-bromo-piridin-2-ilamina (**38**, 4.05 g g, 23.4 mmol) se combinó con 70.0 ml de acetonitrilo, 2-fluoro-benzaldehído (**39**, 2.45 ml, 23.4 mmol), trietilsilano (20.0 ml, 125 mmol) y ácido trifluoroacético (10.0 ml, 130 mmol). La reacción se agitó a 80 °C durante 3 horas. La reacción se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-60% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**40**, 5.0g).

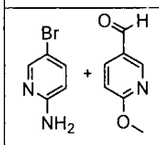
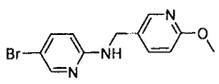
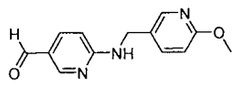
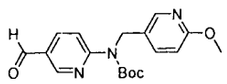
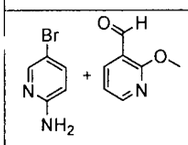
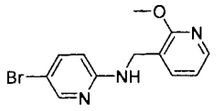
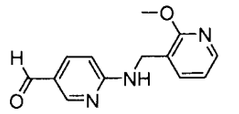
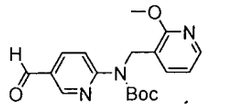
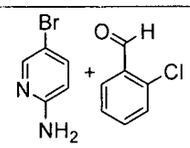
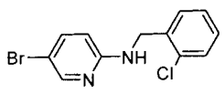
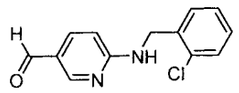
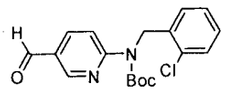
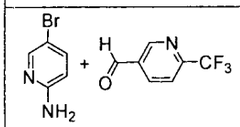
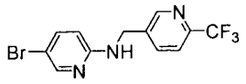
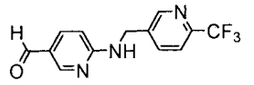
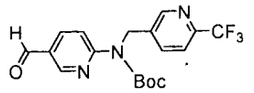
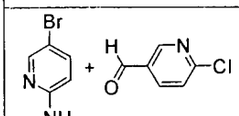
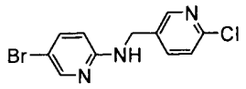
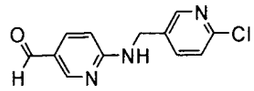
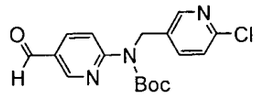
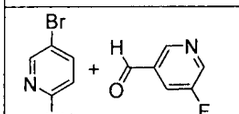
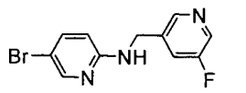
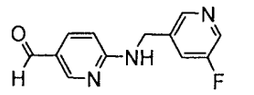
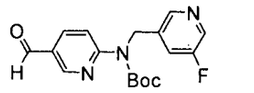
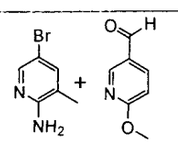
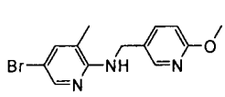
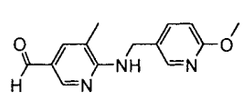
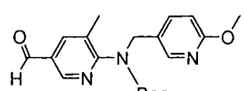
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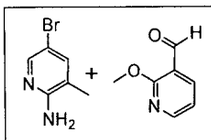
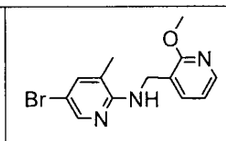
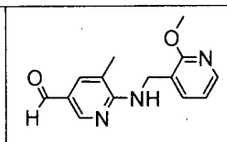
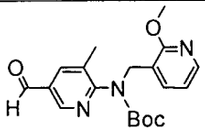
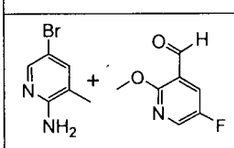
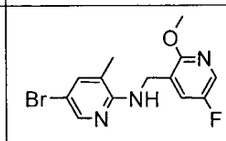
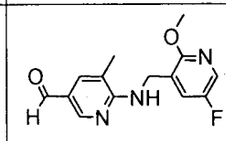
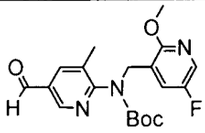
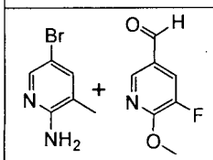
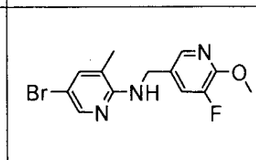
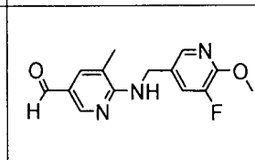
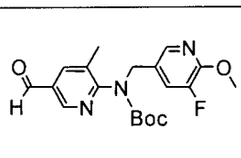
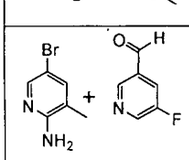
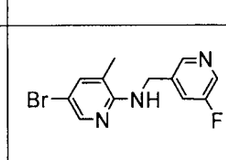
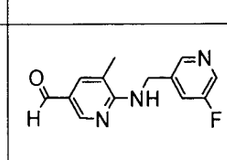
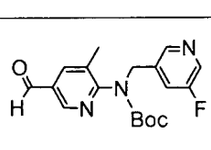
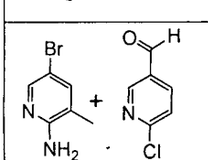
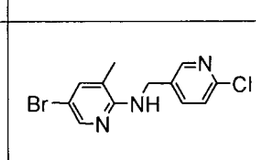
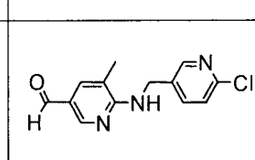
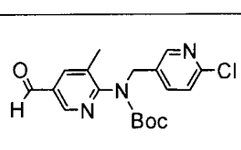
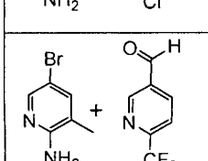
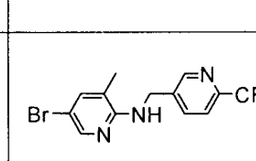
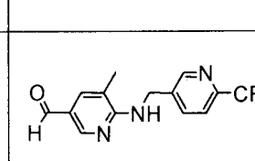
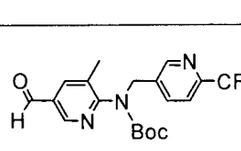
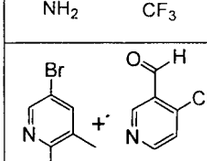
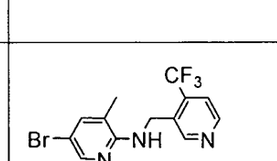
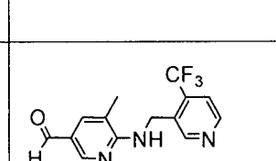
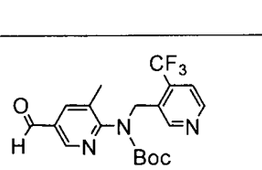
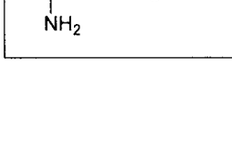
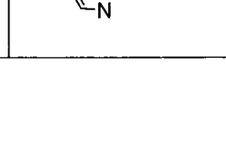
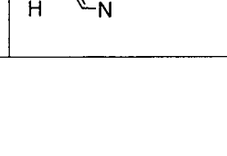
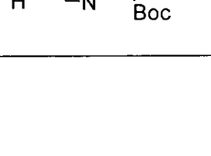
[0280] En un matraz de fondo redondo, (5-bromo-piridin-2-il)-(2-fluoro-bencil)-amina (**40**, 3.90 g, 13.9 mmol) se combinó con 60.0 ml de tetrahidrofurano a -78 °C bajo nitrógeno y ter-butilitio (5.57 ml, 2.50 M en hexano) se agregó durante 5 minutos. Después de 30 minutos ter-butilitio adicional (17.1 ml, 1.7 M en hexano) se agregó durante 5 minutos. Después de 25 minutos, N,N-dimetilformamida (2.6 ml, 34 mmol) se agregó y la mezcla se agitó durante 70 minutos a -78 °C, luego se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La porción orgánica se secó con sulfato de sodio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado (**41**, 3.0 g), el cual se usó en la siguiente etapa sin purificación adicional.

*Etapa 3 – Preparación de ter-butiléster del ácido (2-Fluoro-bencil)-(5-formil-piridin-2-il)-carbámico (**42**):*

[0281] A 6-(2-fluoro-bencilamino)-piridin-3-carbaldehído (**41**, 3.00 g, 13.0 mmol) en 57.2 ml de tetrahidrofurano, di-ter-butildicarbonato (**25**, 4.26 g, 19.5 mmol) y 4-dimetilaminopiridina (0.16 g, 1.3 mmol) y trietilamina (3.6 ml, 26 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La porción orgánica se secó con sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para dar el compuesto deseado (**41**, 3.50 g).

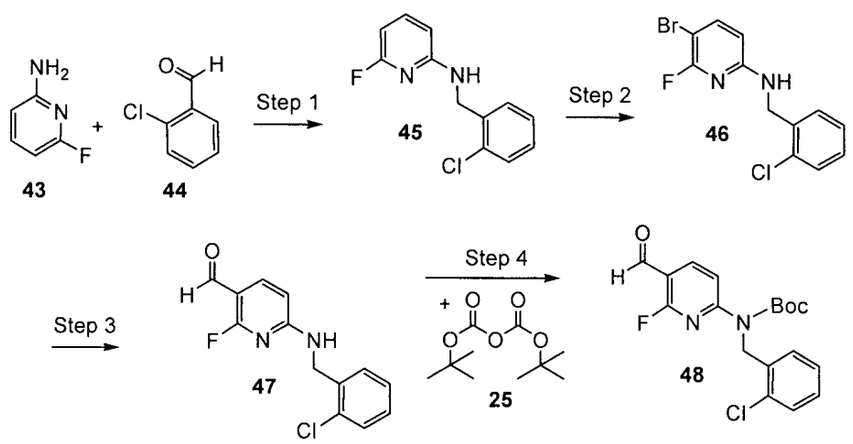
[0282] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10c, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1, Etapa 2 y Etapa 3 se proporcionan en las columnas 1, 2, y 3, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 4. Las condiciones de reacción son similares a aquellas descritas para el Esquema 10c, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Por ejemplo, sin limitación, para la etapa 2, la primera adición de t-butilitio se reemplaza con n-butilitio en pentano o por cloruro de isopropilmagnesio en tetrahidrofurano; para la etapa 3, trietilamina se reemplaza con N,N-diisopropiletilamina, o diclorometano se usa como solvente. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

Etapa 1	Etapa 2	Etapa 3	Aldehído final
			
			
			
			
			
			
			

[0283] ter-butiléster del ácido (2-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico **48** se preparó en cuatro etapas a partir de 6-fluoro-piridin-2-ilamina **43** y 2-cloro-benzaldehído **44** como se muestra en el Esquema 10d.

Esquema 10d



*Etapa 1 – Preparación de (2-cloro-bencil)-(6-fluoro-piridin-2-il)-amina (**45**):*

[0284] A 6-fluoro-piridin-2-ilamina (**43**, 2.47 g, 22.0 mmol) en 60.0 ml de acetonitrilo, 2-cloro-benzaldehído (**44**, 3.09 g, 22.0 mmol), trietilsilano (14.0 ml, 87.6 mmol) y ácido trifluoroacético (7.00 ml, 90.9 mmol) se agregaron. La reacción se agitó a 80 °C durante 4 horas, luego los solventes se removieron bajo vacío, y el residuo se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado, el cual se usó en la siguiente etapa sin purificación adicional. MS (ESI) $[M+H^+]^+ = 272.1$.

*Etapa 2 – Preparación de (5-bromo-6-fluoro-piridin-2-il)-(2-cloro-bencil)-amina (**46**):*

[0285] A (2-cloro-bencil)-(6-fluoro-piridin-2-il)-amina (**45**, 4.70 g, 19.8 mmol) en 100.0 ml de acetonitrilo, N-bromosuccinimida (3.53 g, 19.8 mmol) en 20.0 ml de acetonitrilo se agregó lentamente a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 4 horas, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se lavó con acetato de etilo en hexano para proporcionar el compuesto deseado (**46**, 5.0 g).

*Etapa 3 – Preparación de 6-(2-cloro-bencilamino)-2-fluoro-piridin-3-carbaldehído (**47**):*

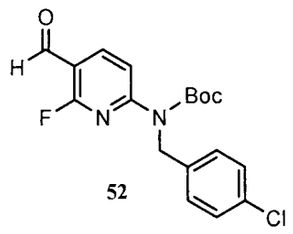
[0286] A (5-bromo-6-fluoro-piridin-2-il)-(2-cloro-bencil)-amina (**46**, 1.85 g, 5.86 mmol) en 25.0 ml de tetrahidrofurano bajo nitrógeno a -78 °C, cloruro de isopropilmagnesio (3.00 ml, 2.00 M en tetrahidrofurano, 6.00 mmol) se agregó durante 10 minutos. Después de 50 minutos, ter-butilitio (7.80 ml, 1.70 M en hexano, 13.3 mmol) se agregó durante 5 minutos. Después de 20 minutos, N,N-dimetilformamida (1.09 ml, 14.0 mmol) se agregó y la mezcla de reacción se agitó a -78 °C durante 20 minutos, luego se llevó a temperatura ambiente durante 30 minutos. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 35% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el

compuesto deseado (**47**, 1.45 g). MS (ESI) $[M+H^+]^+ = 265.4$.

*Etapa 4 – Preparación de ter-butiléster del ácido (2-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico (**48**):*

[0287] A 6-(2-cloro-bencilamino)-2-fluoro-piridin-3-carbaldehído (**47**, 1.45 g, 5.48 mmol) en 31.4 ml de tetrahidrofurano, di-ter-butildicarbonato (**25**, 1.79 g, 8.22 mmol) y 4-dimetilaminopiridina (78.6 mg, 0.643 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 3 horas, luego se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 15-35% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado como un aceite incoloro (**48**, 1.60 g).

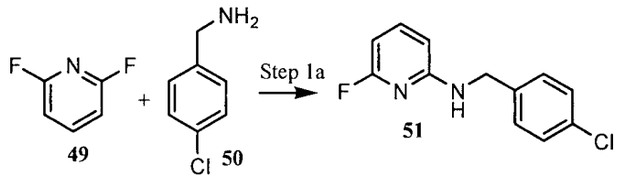
[0288] ter-butiléster del ácido (4-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico **52**



52

se preparó de manera similar al protocolo del Esquema 10d, con la primera etapa modificada al hacer reaccionar 2,6-difluoro-piridina **49** y 4-cloro-bencilamina **50** de acuerdo con la siguiente etapa 1a.

Esquema 10d Etapa 1a

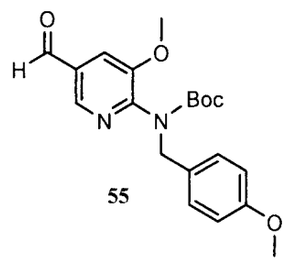


49 **50** **51**

*Etapa 1 – Preparación de (4-cloro-bencil)-(6-fluoro-piridin-2-il)-amina (**51**):*

[0289] A 2,6-difluoro-piridina (**49**, 3.80 g, 33.0 mmol) en 20.0 ml de N-metilpirrolidona, 4-cloro-bencilamina (**50**, 5.6 ml, 46.0 mmol) y N,N-diisopropiletilamina (10.0 ml, 57.4 mmol) se agregaron. La reacción se agitó a 90 °C durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 25% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío, y el material resultante se lavó con acetato de etilo/hexano para proporcionar el compuesto deseado como un sólido blanco (**51**, 5.30 g).

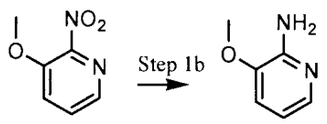
[0290] 3-metoxi-piridin-2-ilamina **54**, para su uso en la etapa 1 del Esquema 10d en la preparación de ter-butiléster del ácido (5-formil-3-metoxi-piridin-2-il)-(4-metoxi-bencil)-carbámico **55** .



55

se preparó en una etapa a partir de 3-metoxi-2-nitro-piridina **53** por la siguiente etapa 1b.

Esquema 10d Etapa 1b



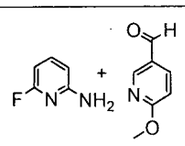
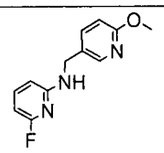
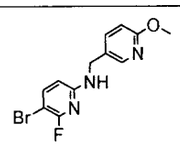
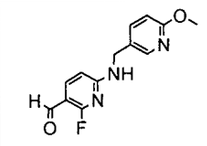
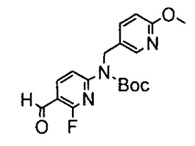
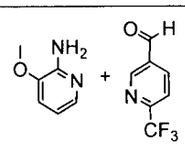
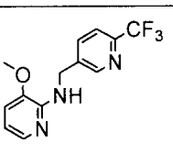
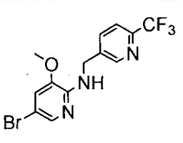
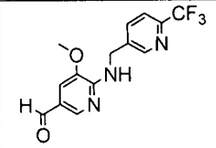
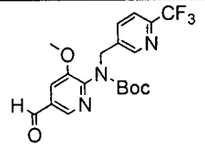
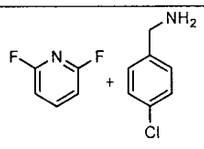
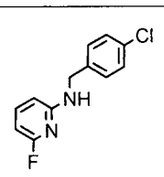
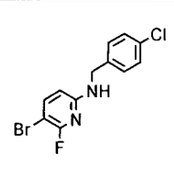
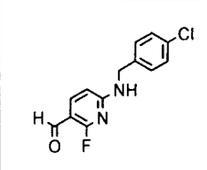
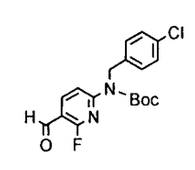
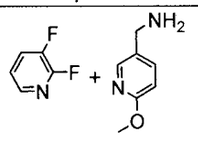
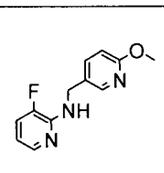
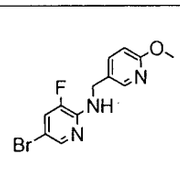
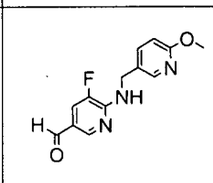
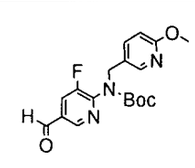
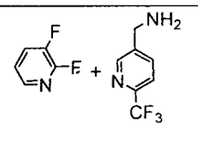
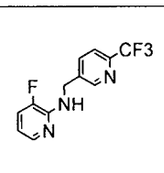
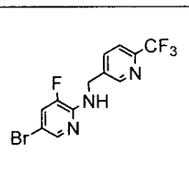
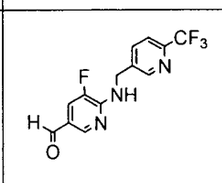
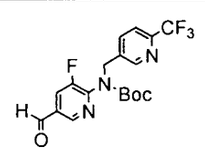
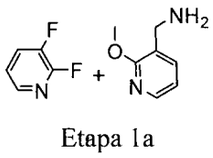
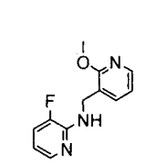
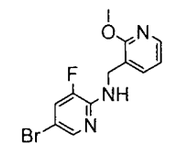
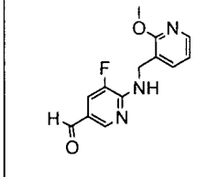
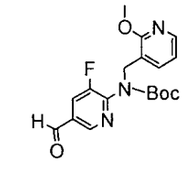
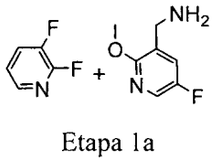
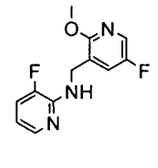
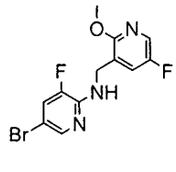
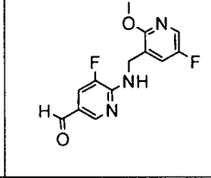
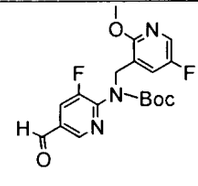
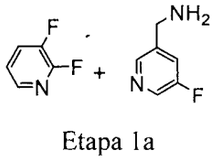
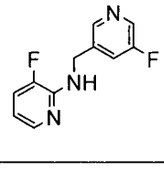
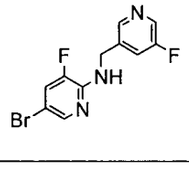
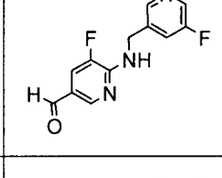
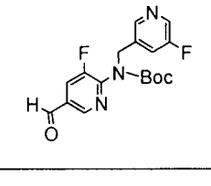
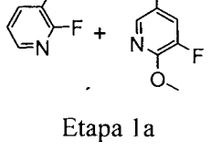
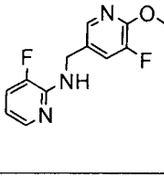
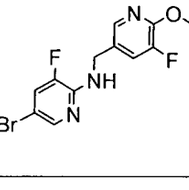
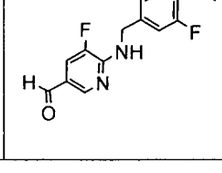
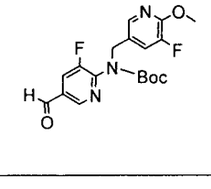
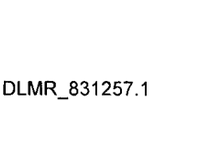
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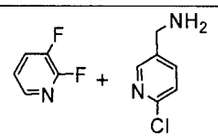
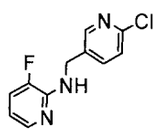
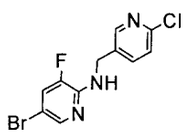
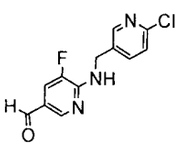
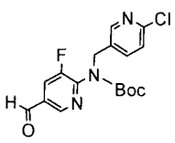
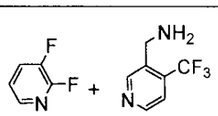
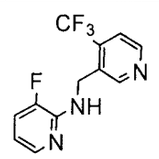
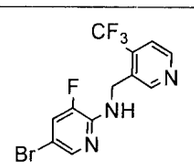
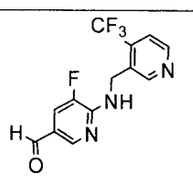
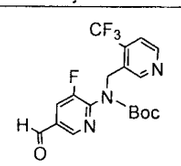
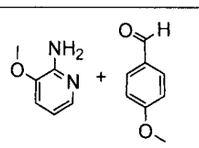
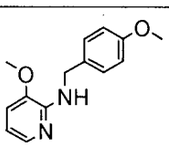
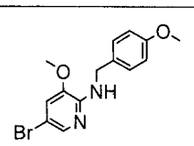
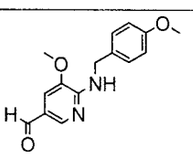
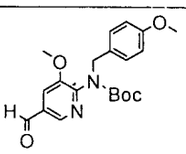
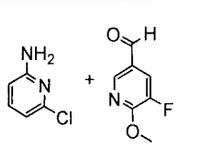
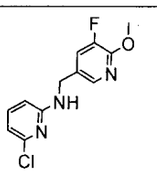
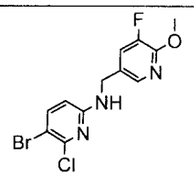
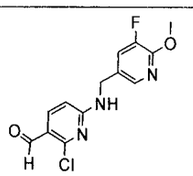
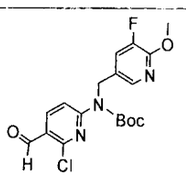
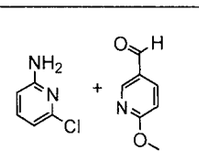
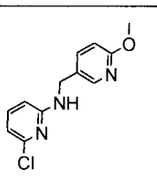
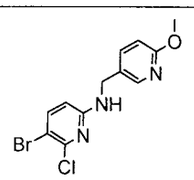
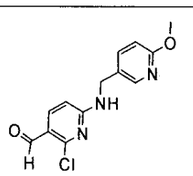
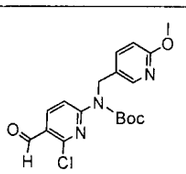
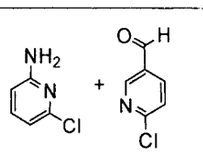
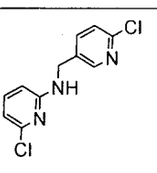
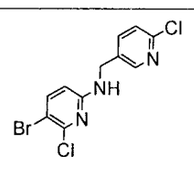
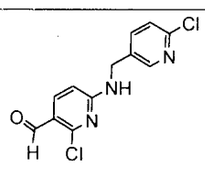
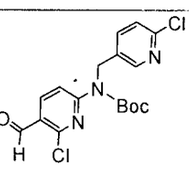
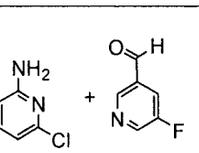
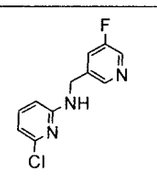
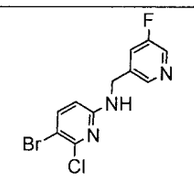
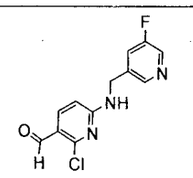
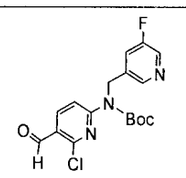
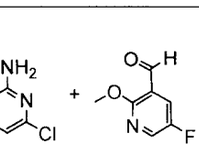
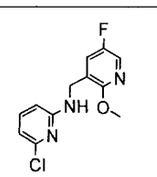
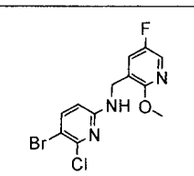
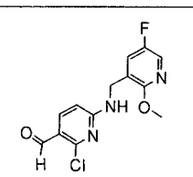
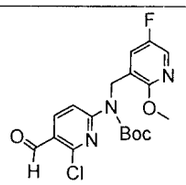
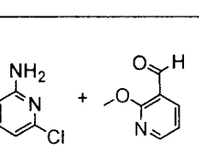
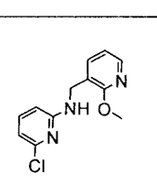
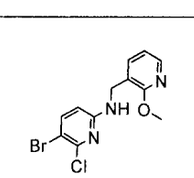
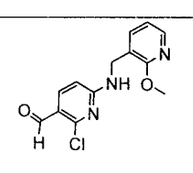
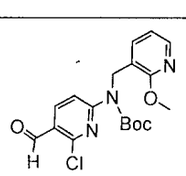
*Etapa 1 – Preparación de 3-metoxi-piridin-2-ilamina (**54**):*

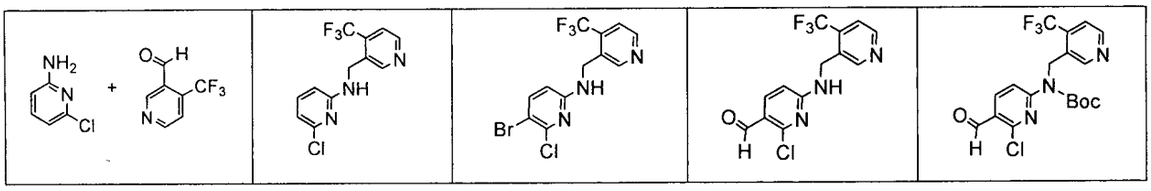
[0291] 3-Metoxi-2-nitro-piridina (**53**, 7.00 g, 45.4 mmol) en 100 ml de metanol, se desgasificó y paladio (0.7 g, 20%) se agregó. La reacción se agitó a temperatura ambiente durante un día bajo un globo de hidrógeno. La reacción se filtró a través de celite y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado (**54**, 5.555 g). MS (ESI) $[M+H^+]^+ = 125.3$.

[0292] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10d, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1 (o 1a), Etapa 2, Etapa 3 y Etapa 4 se proporcionan en las columnas 1, 2, 3, y 4, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 5. En la Etapa 1a un uso se indica en la columna 1. Las condiciones de reacción son similares a aquellas descritas para el Esquema 10d, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Por ejemplo, sin limitación, para la etapa 1a, no se usa N,N-diisopropiletilamina; para la etapa 3, la adición de cloruro de isopropilmagnesio se reemplaza con n-butilitio en hexano; para la etapa 4, trietilamina se incluye en la reacción y diclorometano se usa como solvente. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

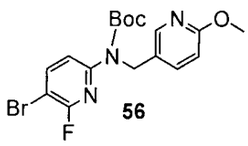
Etapa 1	Etapa 2	Etapa 3	Etapa 4	Aldehído final

				
				
 Etapa 1a				
 Etapa 1a				
 Etapa 1a				
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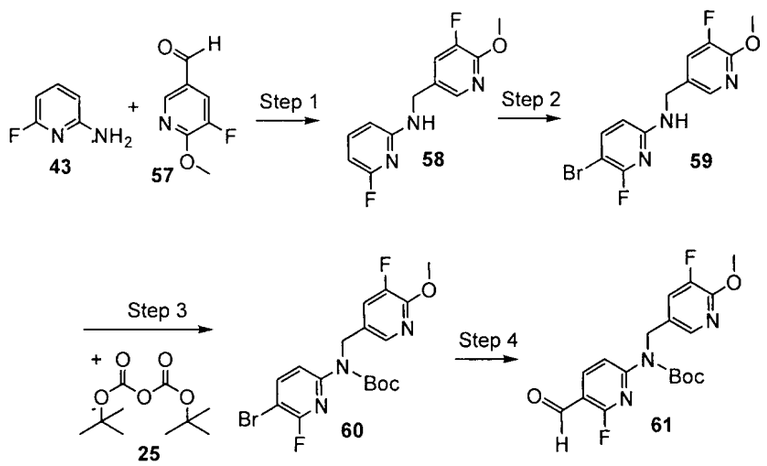
[0293] ter-butiléster del ácido (5-Bromo-6-fluoro-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **56**



se preparó a partir del producto de la etapa 2 para la primera entrada de la tabla, el cual luego fue protegido con Boc de manera similar al protocolo del Esquema 10d etapa 4.

[0294] ter-butiléster del ácido (6-Fluoro-5-formil-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-carbámico **61** se preparó en cuatro etapas a partir de 6-fluoro-piridin-2-ilamina **43** y 5-fluoro-6-metoxi-piridin-3-carbaldehído **57** como se muestra en el Esquema 10e.

Esquema 10e



*Etapa 1 – Preparación de (5-fluoro-6-metoxi-piridin-3-ilmetil)-(6-fluoro-piridin-2-il)-amina (**58**):*

[0295] A 6-fluoro-piridin-2ilamina (**43**, 1.50 g, 13.4 mmol) en 52.9 ml de acetonitrilo, 5-fluoro-6-metoxi-piridin-3-carbaldehído (**57**, 2.00 g, 12.9 mmol), trietilsilano (10.6 ml, 66.3 mmol), y ácido trifluoroacético (5.3 ml, 69.0 mmol) se agregaron. La reacción se agitó a 80 °C durante la noche, luego se concentró bajo vacío, se combinó con agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 15-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para

proporcionar el compuesto deseado como sólido blanco (**58**, 3.21 g).

*Etapa 2 – Preparación de (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**59**):*

[0296] A (5-fluoro-6-metoxi-piridin-3-ilmetil)-(6-fluoro-piridin-2-il)-amina (**58**, 3.21 g, 12.8 mmol) en 100 ml de acetonitrilo, N-bromosuccinimida (2.30 g, 12.9 mmol) en 30 ml de acetonitrilo se agregó lentamente a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 4 horas, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**59**, 3.60 g).

*Etapa 3 – Preparación de ter-butiléster del ácido (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-carbámico (**60**):*

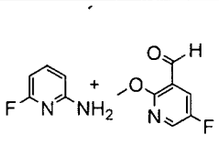
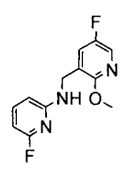
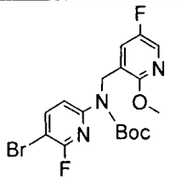
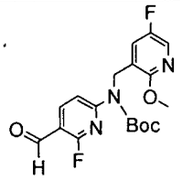
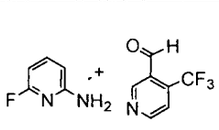
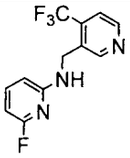
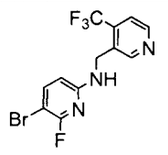
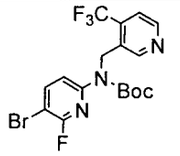
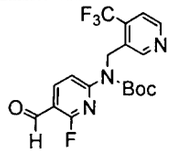
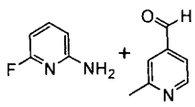
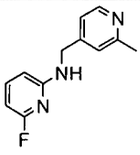
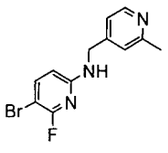
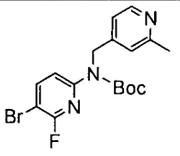
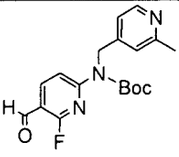
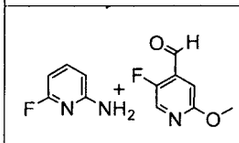
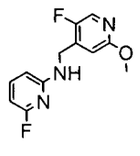
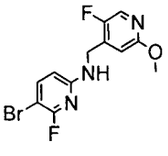
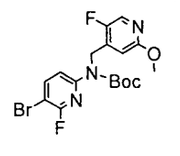
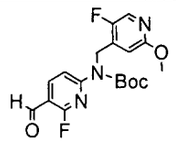
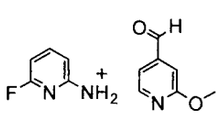
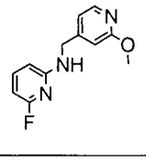
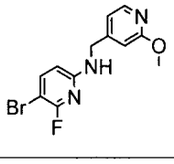
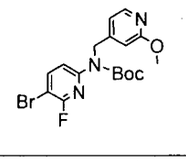
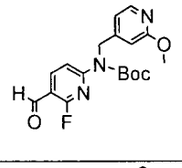
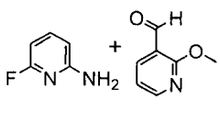
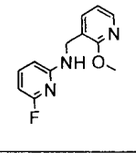
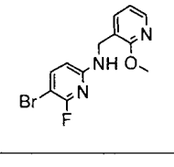
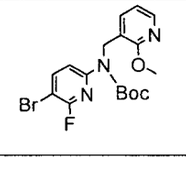
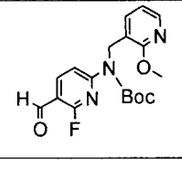
[0297] A (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**59**, 2.70 g, 8.18 mmol) en 58.7 ml de tetrahidrofurano, di-ter-butildicarbonato (**25**, 2.2 g, 9.9 mmol) y 4-dimetilaminopiridina (0.29 g, 2.4 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 90 minutos, luego se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un aceite incoloro (**60**, 3.0 g).

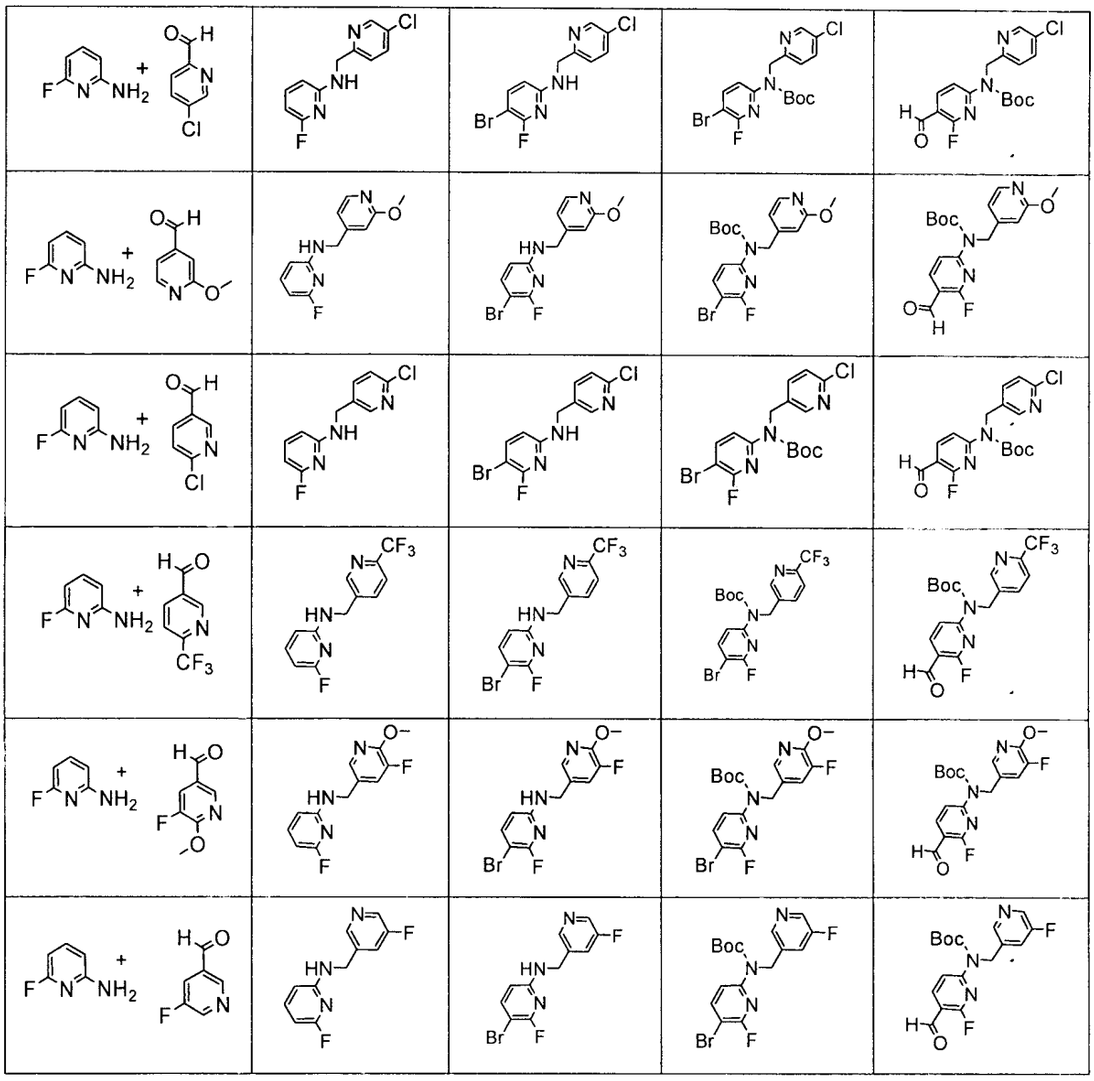
*Etapa 4 – Preparación de ter-butiléster del ácido (6-Fluoro-5-formil-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-carbámico (**61**):*

[0298] A ter-butiléster del ácido (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-6-metoxi-piridin-3-ilmetil)-carbámico (**60**, 2.90 g, 6.74 mmol) en 25.0 ml de tetrahidrofurano a -35 °C bajo nitrógeno, cloruro de isopropilmagnesio (3.54 ml, 2.00 M en tetrahidrofurano, 7.08 mmol) se agregó y la reacción se dejó llegar a 0 °C durante una hora. La reacción se enfrió a -45 °C y N,N-dimetilformamida (1.0 ml, 13.0 mmol) se agregó. La reacción se dejó calentar a temperatura ambiente durante 2 horas, luego se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**61**, 1.80 g).

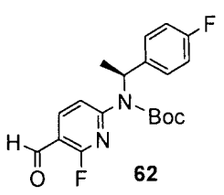
[0299] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10e, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1, Etapa 2, Etapa 3 y Etapa 4 se

proporcionan en las columnas 1, 2, 3, y 4, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 5. En algunos casos, el compuesto deseado es el compuesto de bromo protegido con Boc, aislado después de la etapa 3 para su uso en reacciones subsecuentes. Las condiciones de reacción son similares a aquellas descritas para el Esquema 10e, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Por ejemplo, sin limitación, la etapa 2 se realiza bajo nitrógeno; etapa 3 incluye N,N-diisopropiletilamina. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

Etapa 1	Etapa 2	Etapa 3	Etapa 4	Aldehído final
				
				
				
				
				
				



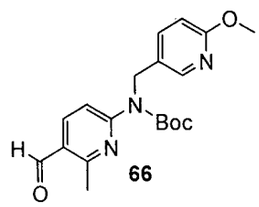
[0300] ter-butiléster del ácido (6-Fluoro-5-formil-piridin-2-il)-[(S)-1-(4-fluoro-fenil)-etil]-carbámico **62**



62

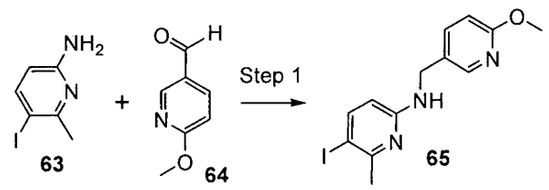
se preparó a partir de 2,6-difluoro-piridina **49** y (S)-1-(4-fluoro-fenil)-etilamina de manera similar al protocolo de la etapa 1a del Esquema 10d, luego las etapas 2-4 del Esquema 10e. La Etapa 3 también incluyó N,N-diisopropiletilamina, así como una adición subsecuente de di-ter-butildicarbonato y N,N-diisopropiletilamina.

[0301] ter-butiléster del ácido (5-Formil-6-metil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **66**



se preparó al hacer reaccionar (5-yodo-6-metil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-amina **65** de manera similar al protocolo del Esquema 10e, etapas 3 y 4, donde la etapa 3 incluyó N,N-diisopropiletilamina. (5-Yodo-6-metil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-amina **65** se preparó en una etapa a partir de 5-yodo-6-metil-piridin-2-ilamina **63** y 6-metoxi-piridin-3-carbaldehído **64** como se muestra en el Esquema 10f.

Esquema 10f

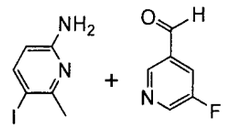
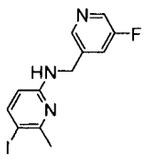
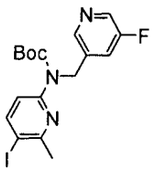
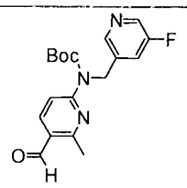
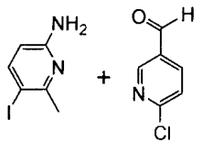
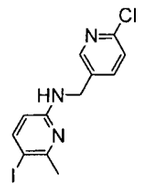
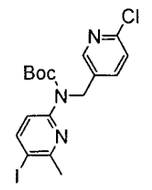
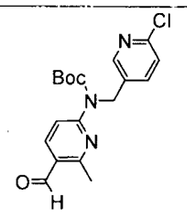
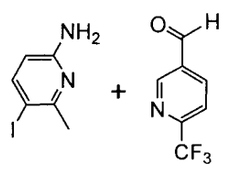
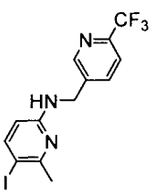
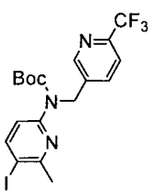
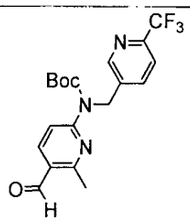
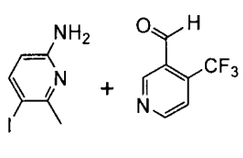
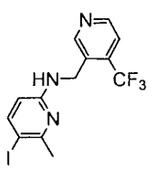
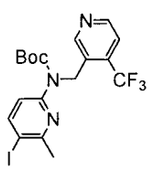
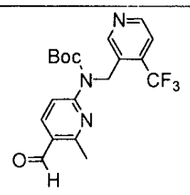
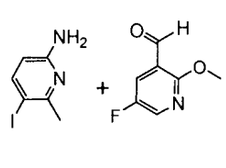
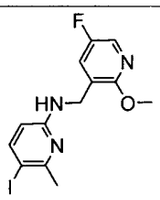
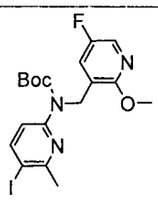
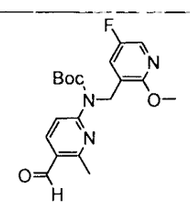
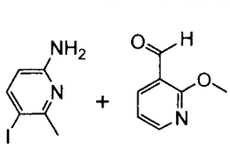
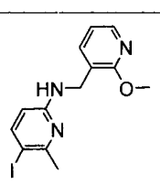
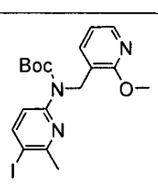
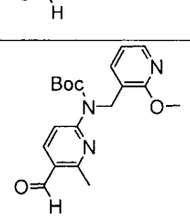
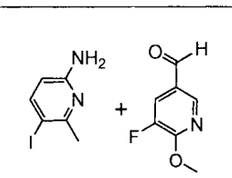
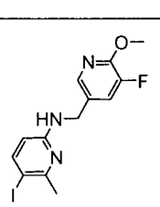
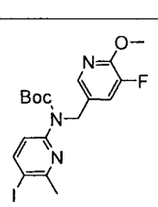
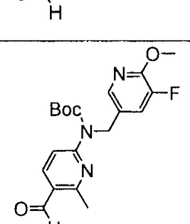


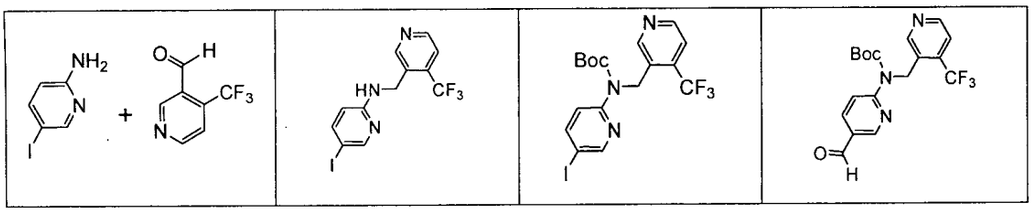
Etapa 1 – Preparación de (5-yodo-6-metil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-amina (65):

[0302] 5-Yodo-6-metil-piridin-2-ilamina (**63**, 1.7 g, 7.3 mmol) y 6-metoxi-piridin-3-carbaldehído (**64**, 1.1 g, 8.0 mmol) se combinaron en un matraz de fondo redondo con ácido trifluoroacético (2.80 ml, 36.3 mmol), trietilsilano (5.80 ml, 36.3 mmol) y 50 ml de acetonitrilo. La reacción se agitó a temperatura ambiente durante la noche, luego calentado a reflujo durante 6 horas. La reacción se concentró bajo vacío, se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna instantánea en gel de sílice, eluyendo con 10-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**65**, 1.80 g). MS (ESI)$[M+H^+]^+$ = 356.80.

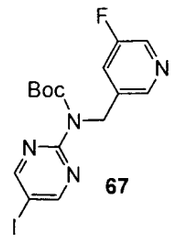
[0303] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10f seguido por el Esquema 10e etapas 2 y 3, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1 (Esquema 10f), Etapa 3 y Etapa 4 se proporcionan en las columnas 1, 2, y 3, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 5. Las condiciones de reacción son similares a aquellas descritas para los Esquemas 10e y 10f, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando

solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica.

Etapa 1	Etapa 3	Etapa 4	Aldehído final
			
			
			
			
			
			
			



[0304] ter-butiléster del ácido (5-fluoro-piridin-3-ilmetil)-(5-yodo-pirimidin-2-il)-carbámico **67**

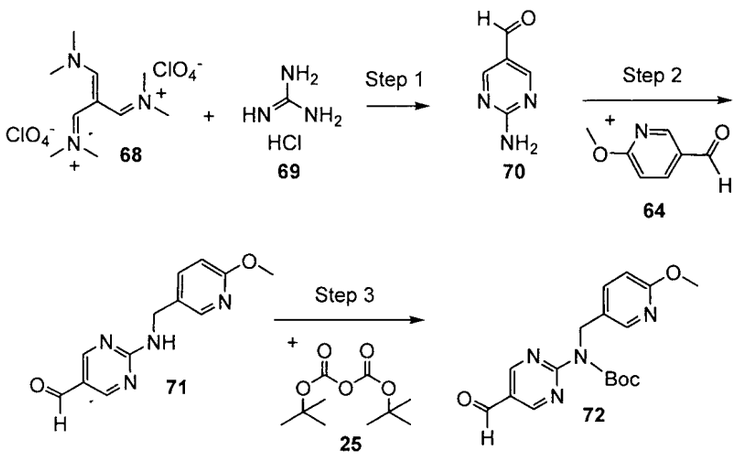


67

se preparó de manera similar al Esquema 10f, reemplazando 5-yodo-6-metil-piridin-2-ilamina **63** con 5-yodo-pirimidin-2-ilamina y 6-metoxi-piridin-3-carbaldehído **64** con 5-fluoro-piridin-3-carbaldehído y protegiendo con Boc el nitrógeno, por ejemplo, siguiendo un protocolo similar al Esquema 10e, etapa 3.

[0305] ter-butiléster del ácido (5-Formil-pirimidin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **72** se preparó en tres etapas a partir de sal vinamidinio **68** y clorhidrato de guanidina **69** como se muestra en el Esquema 10g.

Esquema 10g



Etapa 2 – Preparación de 2-amino-pirimidin-5-carbaldehído (70):

[0306] La sal vinamidinio (**68**, 158 g, 413 mmol) y clorhidrato de guanidina (**69**, 63.3 g, 455 mmol) se disolvieron en 527 ml de acetonitrilo y se enfriaron en un baño de hielo/agua. Hidróxido de sodio

(66.1 ml, 50% p/p, 827 mmol) se agregó por goteo, manteniendo la temperatura por debajo de 25 °C. La reacción se dejó calentar a 25 °C y se agitó durante 4 horas, luego se diluyó con agua y se filtró, se derivó de etanol/heptano, luego se trituró con heptano. El sólido resultante se secó bajo vacío para proporcionar el compuesto deseado (**70**, 37 g, 301 mmol, 72.7% de rendimiento).

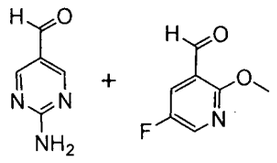
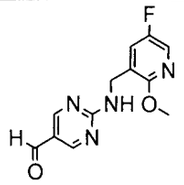
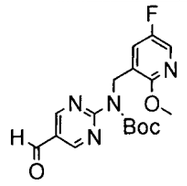
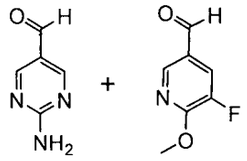
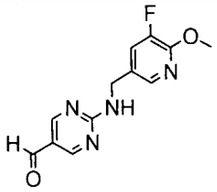
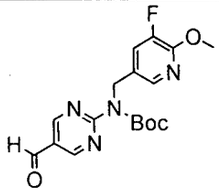
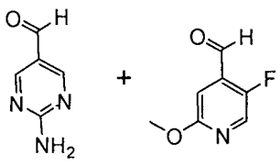
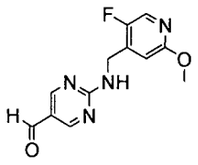
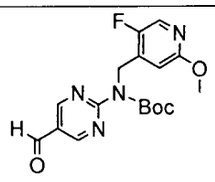
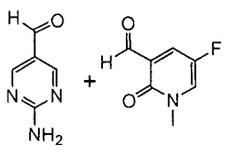
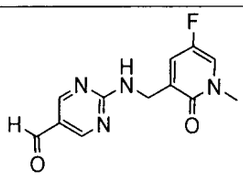
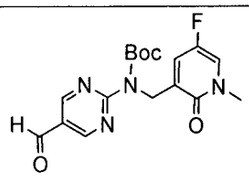
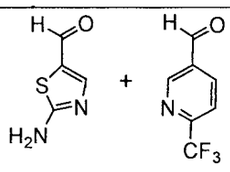
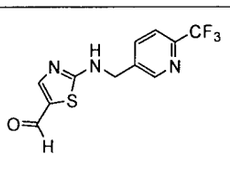
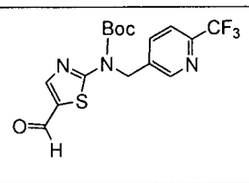
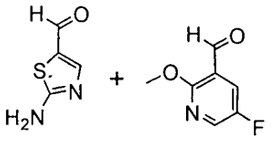
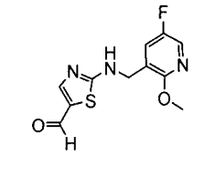
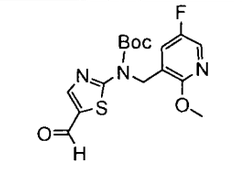
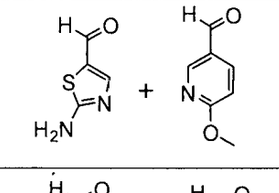
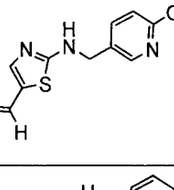
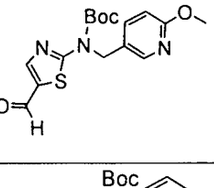
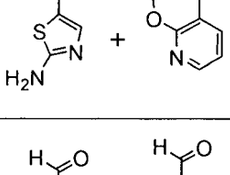
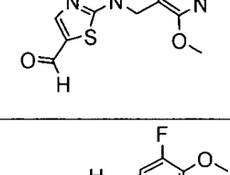
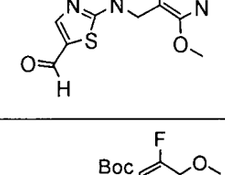
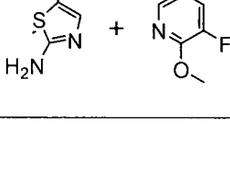
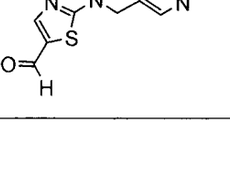
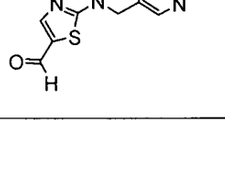
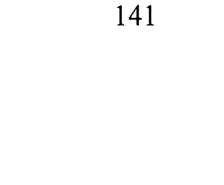
*Etapa 2 – Preparación de 2-[(6-metoxi-piridin-3-ilmetil)-amino]-pirimidin-5-carbaldehído (**71**):*

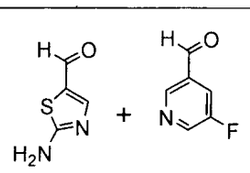
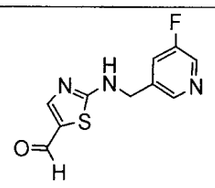
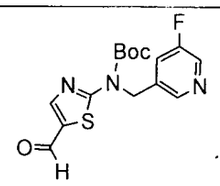
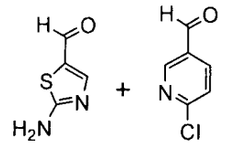
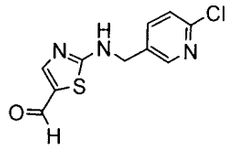
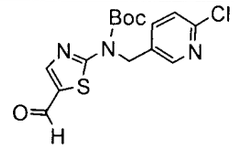
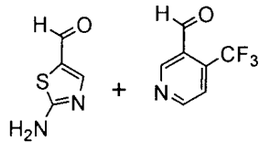
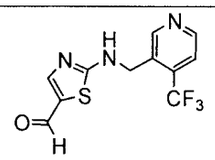
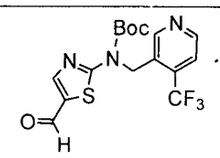
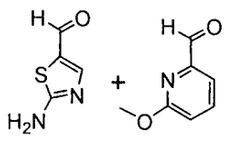
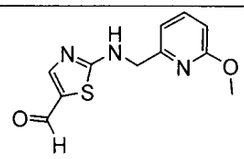
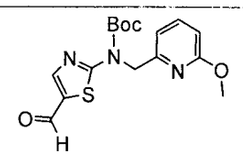
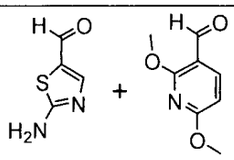
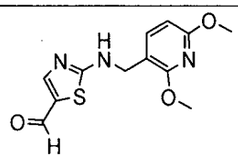
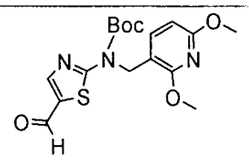
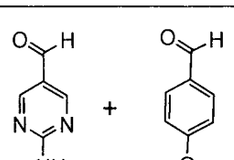
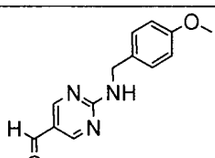
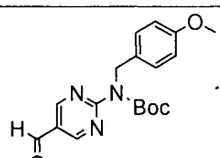
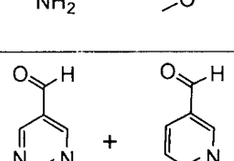
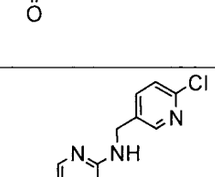
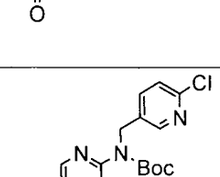
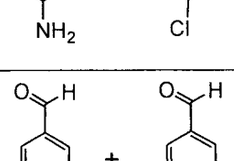
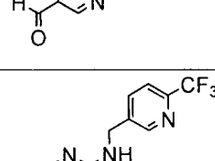
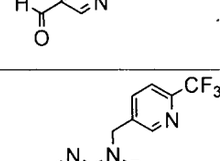
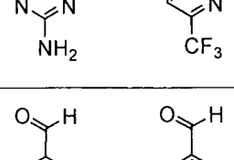
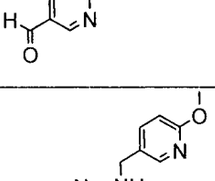
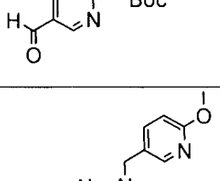
[0307] En un matraz de fondo redondo, 2-amino-pirimidin-5-carbaldehído (**70**, 0.750 g, 6.09 mmol), 6-metoxi-piridin-3-carbaldehído (**64**, 1.67 g, 12.2 mmol), ácido trifluoroacético (2.5 ml, 32.0 mmol), y trietilsilano (5.00 ml, 31.3 mmol) se combinaron con 10 ml de acetonitrilo. La reacción se agitó a temperatura ambiente durante la noche, luego se concentró bajo vacío y se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna instantánea en gel de sílice, eluyendo con 15-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado.

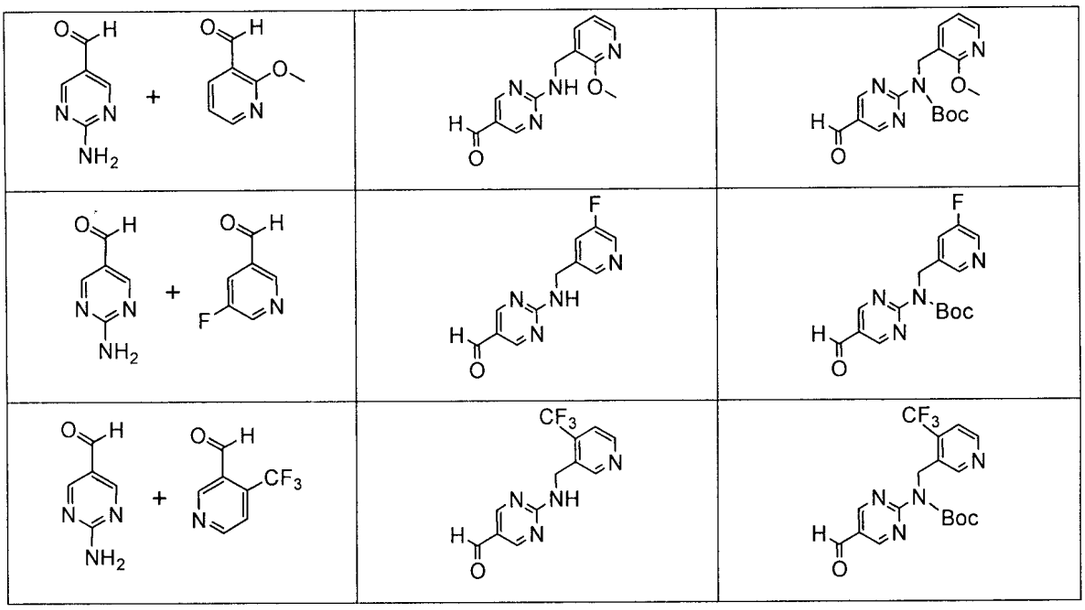
*Etapa 3 – Preparación de ter-butiléster del ácido (5-Formil-pirimidin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico (**72**):*

[0308] A 2-[(6-metoxi-piridin-3-ilmetil)-amino]-pirimidin-5-carbaldehído (**71**, 0.462 g, 1.89 mmol) en 15 ml de tetrahidrofurano, N,N-diisopropiletilamina (0.72 ml, 4.2 mmol), 4-dimetilaminopiridina (0.02 g, 0.2 mmol) y di-ter-butildicarbonato (**25**, 0.45 g, 2.1 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se concentró bajo vacío y el material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado. ^{1}H NMR fue consistente con la estructura del compuesto.

[0309] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10g, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1 y Etapa 2 se proporcionan en las columnas 1 y 2, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 3. Las condiciones de reacción son similares a aquellas descritas para el Esquema 10g, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Por ejemplo, sin limitación, para la etapa 2, N,N-diisopropiletilamina no se incluye en la reacción. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

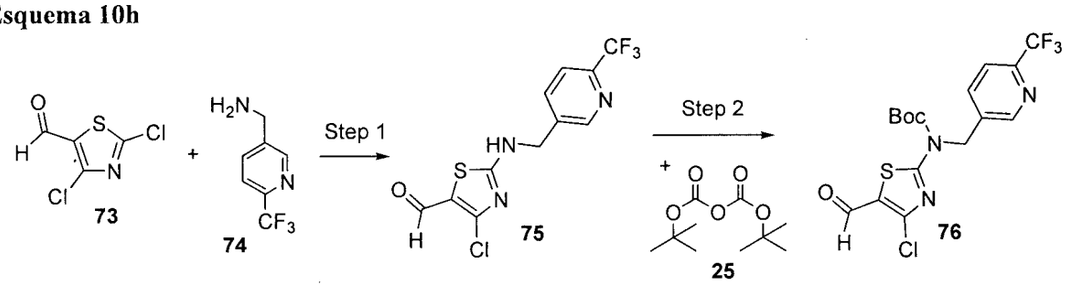
Etapa 1	Etapa 2	Aldehído final
		
		
		
		
		
		
		
		
		
		



[0310] ter-butiléster del ácido (4-Cloro-5-formil-tiazol-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico **76** se preparó en dos etapas a partir de 2,4-dicloro-tiazol-5-carbaldehído **73** y C-(6-trifluorometil-piridin-3-il)-metilamina **74** como se muestra en el Esquema 10h.

Esquema 10h



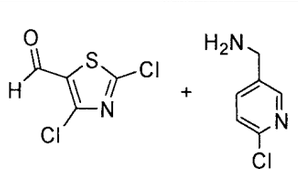
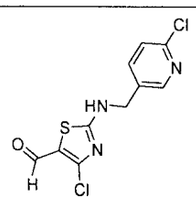
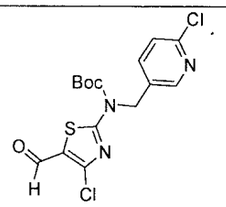
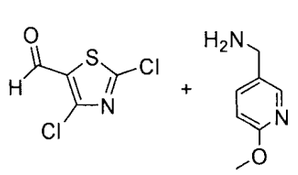
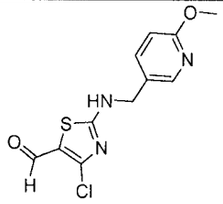
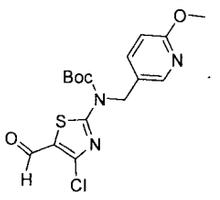
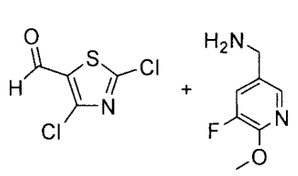
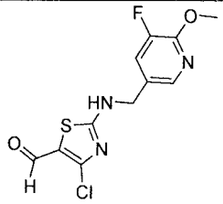
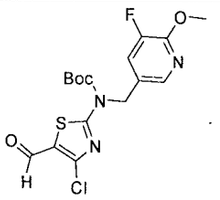
Etapa 1 – Preparación de 4-cloro-2-[(6-trifluorometil-piridin-3-ilmetil)-amino]-tiazol-5-carbaldehído (75):

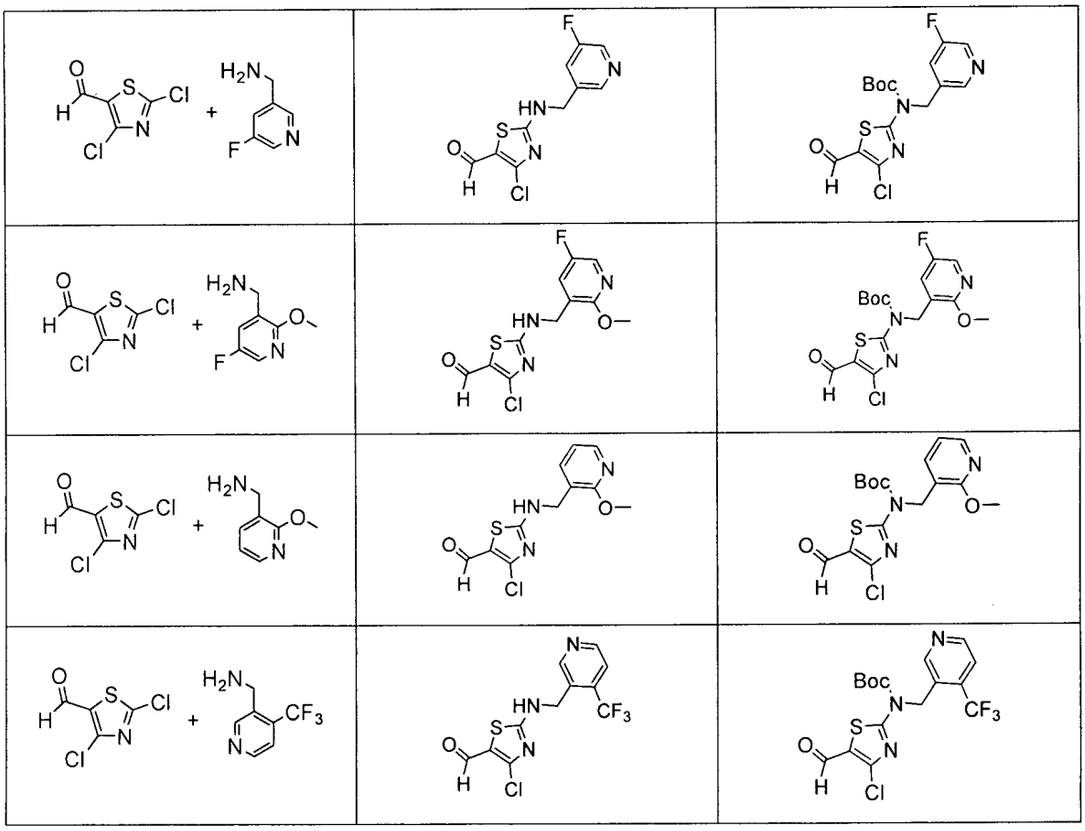
[0311] A una solución de C-(6-trifluorometil-piridin-3-il)-metilamina (**74**, 1.0 g, 5.7 mmol) y N,N-diisopropiletilamina (2.0 ml, 11 mmol) en 100 ml de tetrahidrofurano, 2,4-dicloro-tiazol-5-carbaldehído (**73**, 1.1 g, 6.2 mmol) en 10 ml de tetrahidrofurano se agregó por goteo a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**75**, 1.2 g, 66%). MS (ESI) = $[M+H^+]^+ = 322.11$

*Etapa 2 – Preparación de ter-butiléster del ácido (4-Cloro-5-formil-tiazol-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**76**):*

[0312] 4-Cloro-2-[(6-trifluorometil-piridin-3-ilmetil)-amino]-tiazol-5-carbaldehído (**75**, 1.2 g, 3.7 mmol), di-ter-butildicarbonato (**25**, 0.98 g, 4.5 mol), 4-dimetilaminopiridina (0.09 g, 0.7 mmol) y N,N-diisopropiletilamina (0.96 g, 7.5 mmol) se combinaron en 170 ml de diclorometano y se agitaron a temperatura ambiente durante la noche. La mezcla de reacción se vertió en agua helada, se extrajo con diclorometano, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**76**, 1.5 g, 95%).

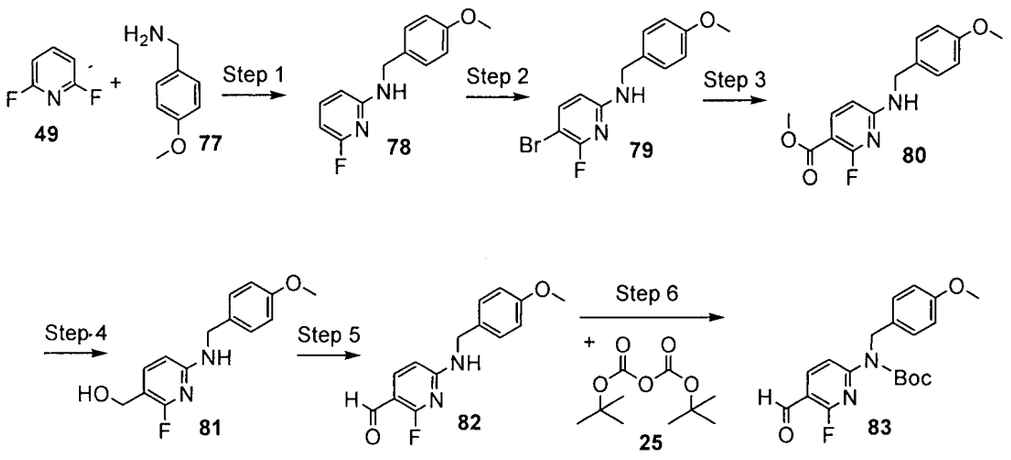
[0313] Aldehídos adicionales se preparan de manera similar al protocolo del Esquema 10h, como se muestra en la siguiente tabla, donde los reactivos de la Etapa 1 y Etapa 2 se proporcionan en las columnas 1 y 2, respectivamente, con el aldehído resultante protegido con Boc proporcionado en la columna 3. Las condiciones de reacción son similares a aquellas descritas para el Esquema 10h, y pueden variar ligeramente para cada etapa, por ejemplo, cualquiera de los solventes, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

Etapa 1	Etapa 2	Aldehído final
		
		
		



[0314] ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico **83** se preparó en seis etapas a partir de 2,6-difluoro-piridina **49** como se muestra en el Esquema 10i.

Esquema 10i



*Etapa 1 – Preparación de (6-fluoro-piridin-2-il)-(4-metoxi-bencil)-amina (**78**):*

[0315] A 2,6-difluoro-piridina (**49**, 100 g, 869 mmol) en 500 ml de N-metilpirrolidinona, 4-metoxi-bencilamina (77, 136 ml, 1.043 mol) y N,N-diisopropiletilamina (304 ml, 1.738 mol) se agregaron.

La reacción se agitó a 90 °C durante la noche, luego se vertió en 8 L de agua. El precipitado se recolectó por filtración y se lavó con agua, luego se recogió en acetato de etilo y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se trituró con heptano y se recolectó por filtración para proporcionar el compuesto deseado (**78**, 151 g, 650 mmol, 74.8 % de rendimiento).

*Etapa 2 – Preparación de (5-bromo-6-fluoro-piridin-2-il)-(4-metoxi-bencil)-amina (**79**):*

[0316] A (6-fluoro-piridin-2-il)-(4-metoxi-bencil)-amina (**78**, 151 g, 650 mmol) en 4 L de acetonitrilo bajo nitrógeno, N-bromosuccinimida (116 g, 650 mmol) se agregó en porciones. Después de reaccionar durante 2 horas, el solvente se removió bajo vacío y el residuo se recogió en acetato de etilo, luego se vertió en tiosulfato de sodio acuoso. La capa orgánica se lavó con agua tibia, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se cristalizó a partir de heptano para proporcionar el compuesto deseado (**79**, 172 g, 553 mmol, 85 % de rendimiento).

*Etapa 3 – Preparación de metiléster del ácido 2-fluoro-6-(4-metoxi-bencilamino)-nicotínico (**80**):*

[0317] A (5-bromo-6-fluoro-piridin-2-il)-(4-metoxi-bencil)-amina (**79**, 85 g, 273 mmol) en 1.5 L de metanol en un matraz Parr de 2 L, trietilamina (77 ml, 546 mmol) y [1,1'-bis(difenilfosfino)ferroceno] dicloropaladio(II) (5.80 g, 7.10 mmol) se agregaron. La reacción se calentó a 100 °C bajo 100 psi de monóxido de carbono durante la noche. La reacción se enfrió y se filtró a través de celite y el filtrado se concentró bajo vacío. El material resultante se disolvió en diclorometano y se pasó a través de un tapón de gel de sílice, eluyendo con acetato de etilo. El solvente se removió bajo vacío para proporcionar el compuesto deseado como un sólido de color durazno (**80**, 70 g, 241 mmol, 88 % de rendimiento).

*Etapa 4 – Preparación de [2-fluoro-6-(4-metoxi-bencilamino)-piridin-3-il]-metanol (**81**):*

[0318] A metiléster del ácido 2-fluoro-6-(4-metoxi-bencilamino)-nicotínico (**80**, 70 g, 241 mmol) en 350 ml de tetrahidrofurano, hidruro de litio y aluminio (362 ml, 1 M en tetrahidrofurano, 362 mmol) se agregó por goteo mientras se enfriaba. La reacción se agitó a temperatura ambiente durante 2 horas, luego se extinguió con adición por goteo de 14 ml de agua, 14 ml de 15% de hidróxido de sodio acuoso, y 42 ml de agua, en secuencia. Metil ter-butil éter (500 ml) se agregó y los sólidos se removieron por filtración. El filtrado se concentró bajo vacío y el sólido resultante se disolvió en diclorometano, se pasó a través de un tapón de gel de sílice y se eluyó con 50-100% de acetato de etilo en heptano. El solvente se removió bajo vacío para proporcionar el compuesto deseado como un sólido blanquecino (**81**, 63 g, 240 mmol, 100 % de rendimiento).

*Etapa 5 – Preparación de 2-fluoro-6-(4-metoxi-bencilamino)-piridin-3-carbaldehído (**82**):*

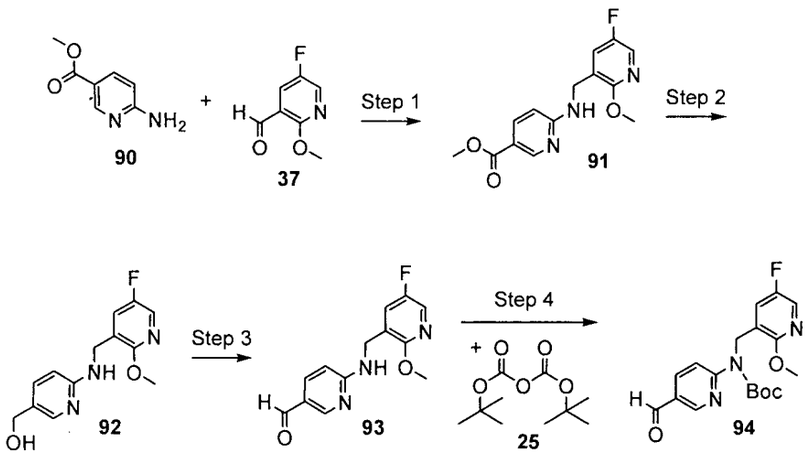
[0319] A [2-fluoro-6-(4-metoxi-bencilamino)-piridin-3-il]-metanol (**81**, 63 g, 240 mmol) en 1.25 L de acetato de etilo, óxido de manganeso(IV) (210 g, 2.416 mol) se agregó. La reacción se agitó durante la noche a temperatura ambiente, luego se filtró a través de celite y el celite se enjuagó con acetato de etilo. Los filtrados combinados se concentraron bajo vacío y el sólido resultante se trituró con heptano y se recolectó por filtración para proporcionar el compuesto deseado como un sólido blanco (**82**, 62 g, 238 mmol, 99% de rendimiento).

Etapa 6 – Preparación de ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico (83):

[0320] 2-Fluoro-6-(4-metoxi-bencilamino)-piridin-3-carbaldehído (**82**, 62 g, 238 mmol), 600 ml de alcohol ter-butílico, di-ter-butildicarbonato (**25**, 83 ml, 357 mmol) y dimetilaminopiridina (2.91 g, 23.82 mmol) se combinaron en un matraz de fondo redondo. La reacción se agitó a 30 °C durante la noche y luego se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**83**, 54 g, 150 mmol, 62.9 % de rendimiento).

[0321] ter-butiléster del ácido (5-Fluoro-2-metoxi-piridin-3-ilmetil)-(5-formil-piridin-2-il)-carbámico **94** se preparó en cuatro etapas a partir de metiléster del ácido 6-amino-nicotínico **90** y 5-fluoro-2-metoxi-piridin-3-carbaldehído **37** como se muestra en el Esquema 10k.

Esquema 10k



Etapa 1 – Preparación de metiléster del ácido 6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-nicotínico (91):

[0322] En un matraz de fondo redondo, metiléster del ácido 6-amino-nicotínico (**90**, 0.678 g, 4.46 mmol) se combinó con 5-fluoro-2-metoxi-piridin-3-carbaldehído (**37**, 0.532 g, 3.43 mmol), 10.6 ml de acetonitrilo, ácido trifluoroacético (1.32 ml, 17.1 mmol) y trietilsilano (3.29 ml, 20.6 mol). La

reacción se calentó a reflujo durante 3 horas, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**91**, 832 mg). MS (ESI) $[M+H^+]^+ = 292.4$.

*Etapa 2 – Preparación de {6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-il}-metanol (**92**):*

[0323] A metiléster del ácido 6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-nicotínico (**91**, 0.825 g, 2.83 mmol) en 11 ml de tetrahidrofurano, tetrahidroaluminato de litio (5.66 ml, 1.0 M en tetrahidrofurano, 5.66 mmol) se agregó a -40 °C bajo nitrógeno. La reacción se dejó calentar a temperatura ambiente y se agitó durante la noche. La reacción se vertió en hidróxido de sodio acuoso 1M, luego se neutralizó con ácido clorhídrico acuoso 1M. Los sólidos se filtraron a través de celite, el celite se lavó con acetato de etilo y tetrahidrofurano. La capa acuosa aislada se extrajo con acetato de etilo y todas las capas orgánicas se combinaron, se lavaron con salmuera, luego se secaron sobre sulfato de sodio, se filtraron y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**92**, 357 mg). MS (ESI) $[M+H^+]^+ = 264.4$.

*Etapa 3 – Preparación de 6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-carbaldehído (**93**):*

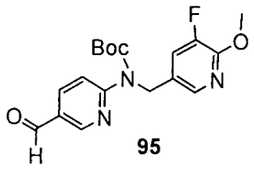
[0324] A {6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-il}-metanol (**92**, 0.353 g, 1.34 mmol) disuelto en 8 ml de tetrahidrofurano, periodinano de Dess-Maritn (0.626 g, 1.47 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 1 hora. La reacción se vertió en tiosulfito de sodio saturado acuoso y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 262.3$.

*Etapa 4 – Preparación de ter-butiléster del ácido (5-Fluoro-2-metoxi-piridin-3-ilmetil)-(5-formil-piridin-2-il)-carbámico (**94**):*

[0325] A 6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-carbaldehído (**93**, 0.310 g, 1.19 mmol) disuelto en 4.72 ml de tetrahidrofurano, 4-dimetilaminopiridina (14.5 mg, 0.119 mmol) se agregó, seguido por di-ter-butildicarbonato (**25**, 0.285 g, 1.30 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las

fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**94**, 301 mg).

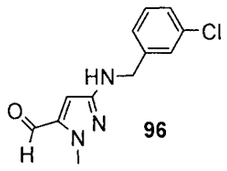
[0326] ter-butiléster del ácido (5-Fluoro-6-metoxi-piridin-3-ilmetil)-(5-formil-piridin-2-il)-carbámico **95**



95

se preparó de manera similar al protocolo del Esquema 10k, reemplazando 5-fluoro-2-metoxi-piridin-3-carbaldehído **37** con 5-fluoro-6-metoxi-piridin-3-carbaldehído en la etapa 1.

[0327] 5-(3-Cloro-bencilamino)-2-metil-2H-pirazol-3-carbaldehído **96**

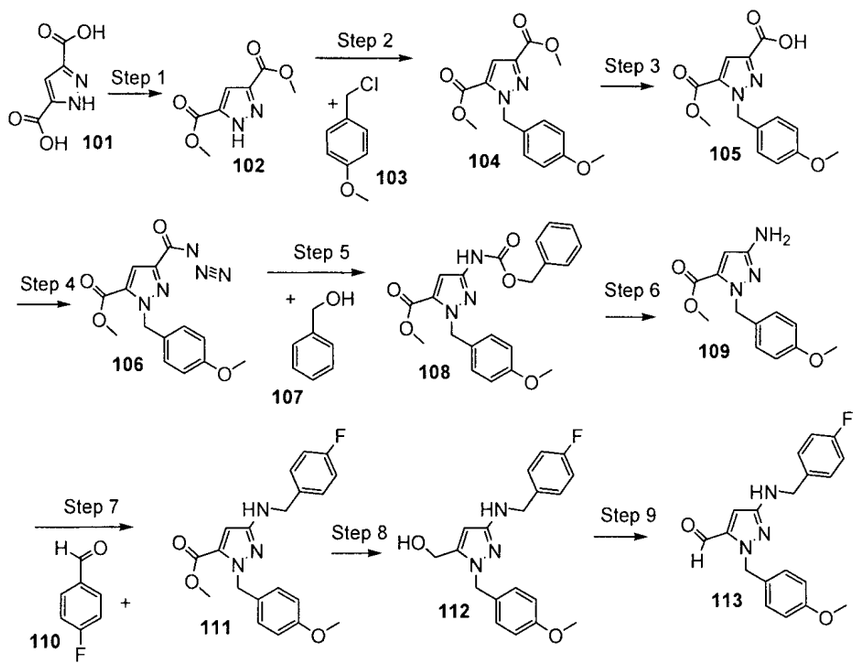


96

se preparó de manera similar al protocolo del Esquema 10k, etapas 1-2 y Esquema 10i, etapa 3, donde metiléster del ácido 6-amino-nicotínico **90** se reemplazó con metiléster del ácido 5-amino-2-metil-2H-pirazol-3-carboxílico y 5-fluoro-2-metoxi-piridin-3-carbaldehído **37** se reemplazó con 3-cloro-benzaldehído en la etapa 1.

[0328] 5-(4-Fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carbaldehído **113** se preparó en nueve etapas a partir de ácido 1H-pirazol-3,5-dicarboxílico **101** como se muestra en el Esquema 10n.

Esquema 10n



*Etapa 1 – Preparación de dimetiléster del ácido 1H-pirazol-3,5-dicarboxílico (**102**):*

[0329] En un matraz de fondo redondo, ácido 1H-pirazol-3,5-dicarboxílico, hidratado (**101**, 21.1 g, 121 mmol) se combinó con 350 ml de metanol y 10 ml de ácido clorhídrico se agregaron. La reacción se agitó a reflujo durante la noche y el siguiente día a temperatura ambiente. La reacción se concentró bajo vacío y el sólido se lavó con acetato de etilo y hexanos para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 185$.

*Etapa 2 – Preparación de dimetiléster del ácido 1-(4-metoxi-bencil)-1H-pirazol-3,5-dicarboxílico (**104**):*

[0330] En un matraz de fondo redondo, dimetiléster del ácido 1H-pirazol-3,5-dicarboxílico (**102**, 15.0 g, 81.4 mmol) se combinó con 1500 ml de acetona y carbonato de potasio (15 g, 110 mmol). 1-Clorometil-4-metoxi-benceno (**103**, 10.0 ml, 73.8 mmol) se agregó y la reacción se agitó a 60 °C durante la noche. La mezcla se separó en dos matraces y continuó agitándose durante 5 horas. Las reacciones se concentraron bajo vacío y los sólidos se lavaron con agua fría y se secaron bajo vacío para proporcionar el compuesto deseado (**104**, 20.48 g). ^{1}H NMR fue consistente con la estructura del compuesto.

*Etapa 3 – Preparación de 5-metiléster del ácido 1-(4-metoxi-bencil)-1H-pirazol-3,5-dicarboxílico (**105**):*

[0331] En un matraz de fondo redondo, dimetiléster del ácido 1-(4-metoxi-bencil)-1H-pirazol-3,5-dicarboxílico (**104**, 28.5 g, 93.6 mmol) se combinó con 100 ml de agua y 20 ml de 1,4-dioxano. Ácido sulfúrico (5.5 ml, 100 mmol) y 2.0 ml de agua se agregaron y la reacción se agitó durante 2

días a 60-70 °C. La reacción se concentró bajo vacío hasta que un precipitado se formó. El sólido se recolectó por filtración y se lavó con agua fría varias veces para proporcionar el compuesto deseado. ^{1}H NMR fue consistente con la estructura del compuesto.

*Etapa 4 – Preparación de metiléster del ácido 5-azidocarbonil-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**106**):*

[0332] En un matraz de fondo redondo, 5-metiléster del ácido 1-(4-metoxi-bencil)-1H-pirazol-3,5-dicarboxílico (**105**, 5.48 g, 18.9 mmol) se combinó con 20 ml de tolueno y cloruro de tionilo (6 ml, 80 mmol). La reacción se calentó a reflujo durante 40 minutos, luego se concentró 2x a partir de tolueno y el sólido resultante se secó bajo vacío. Este se disolvió en 30.0 ml de acetona y azida de sodio (3.8 g, 58 mmol) en 10.0 ml de agua se agregaron y se agitó durante 1 minuto. La reacción se vertió en 250 ml de agua helada y se agitó lentamente. El precipitado resultante se recolectó por filtración y se secó bajo vacío para proporcionar el compuesto deseado.

*Etapa 5 – Preparación de metiléster del ácido 5-benciloxicarbonilamino-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**108**):*

[0333] En un matraz de fondo redondo, metiléster del ácido 5-azidocarbonil-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**106**, 5.6 g, 18.0 mmol) se combinó con 30 ml de tolueno y alcohol bencílico (**107**, 1.91 ml, 18.5 mmol) se agregó y la reacción se calentó a reflujo durante 1 hora. La reacción se concentró bajo vacío y el material resultante se lavó con 2x metanol para proporcionar el compuesto deseado como un sólido blanco. ^{1}H NMR fue consistente con la estructura del compuesto.

*Etapa 6 – Preparación de metiléster del ácido 5-amino-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**109**):*

[0334] En un matraz de fondo redondo, metiléster del ácido 5-benciloxicarbonilamino-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**108**, 2.3 g, 5.8 mmol) se combinó con 30 ml de metanol y 10 ml de tetrahidrofurano bajo nitrógeno y 10% paladio sobre carbono (0.23 g, 13.0 mmol) se agregó. La reacción se agitó bajo hidrógeno a 1 atmósfera durante 2 horas. La reacción se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado (**109**, 1.4 g).

*Etapa 7 – Preparación de metiléster del ácido 5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**111**):*

[0335] En un matraz de fondo redondo, metiléster del ácido 5-amino-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**109**, 1.4 g, 5.4 mmol) se combinó con 4-fluoro-benzaldehído (**110**, 0.565 ml, 5.36 mmol), ácido trifluoroacético (2.06 ml, 26.8 mmol), trietilsilano (4.28 ml, 26.8 mmol) y 50 ml de acetonitrilo. La reacción se agitó a temperatura ambiente durante 15 minutos, luego se concentró bajo vacío, se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El residuo se recristalizó

a partir de un mezcla de acetato de etilo y hexano para proporcionar el compuesto deseado (**111**, 1.6 g). ^{1}H NMR fue consistente con la estructura del compuesto.

Etapa 8 – Preparación de [5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-il]-metanol (112):

[0336] En un matraz de fondo redondo, metiléster del ácido 5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carboxílico (**111**, 1.6 g, 4.3 mmol) se combinó con 100 ml de tetrahidrofurano y se enfrió a -40 °C. Tetrahidroaluminato de litio (4.8 ml, 1.0 M en tetrahidrofurano, 4.8 mmol) se agregó y la reacción se dejó calentar a 10 °C. La reacción se extinguió con sulfato de sodio decahidratado, luego se agitó durante 2 horas, se filtró a través de celite y el filtrado se concentró bajo vacío. El material resultante se lavó con acetato de etilo y hexanos y el sólido se secó para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 342.30$

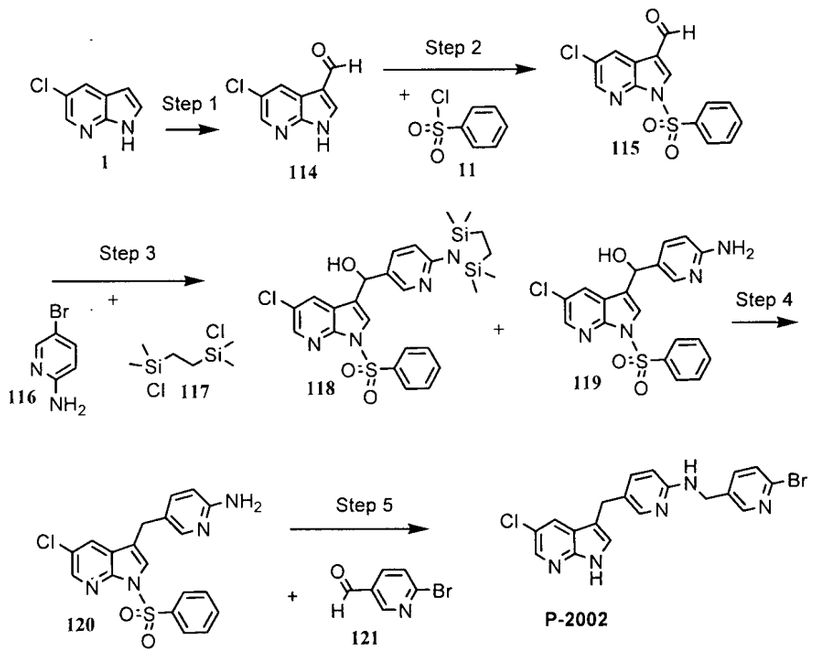
Etapa 9 – Preparación de 5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carbaldehído (113):

[0337] En un matraz de fondo redondo, [5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-il]-metanol (**112**, 1.6 g, 4.2 mmol) se combinó con 300 ml de diclorometano y óxido de manganeso(IV) (0.61 g, 7.0 mmol) y se agitó durante la noche bajo nitrógeno. La reacción se filtró a través de celite y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 10-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**113**, 1.4 g). ^{1}H NMR fue consistente con la estructura del compuesto.

Ejemplo 11: Síntesis de (6-bromo-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-2002.

[0338] (6-Bromo-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-2002** se preparó en cinco etapas a partir de 5-cloro-1H-pirrolo[2,3-b]piridina **1** como se muestra en el Esquema 11.

Esquema 11



*Etapa 1 – Preparación de 5-cloro-1H-pirrolo[2,3-b]piridin-3-carbaldehído (**114**):*

[0339] En un matraz de fondo redondo, 5-cloro-1H-pirrolo[2,3-b]piridina (**1**, 10.0 g, 65.5 mmol) se combinó con hexametilenotetramina (11.9 g, 85.2 mmol), ácido acético (28.3 ml, 0.498 mol) y 56.7 ml de agua. La reacción se calentó a reflujo durante la noche, luego 200 ml de agua se agregaron. Después de 30 minutos, el material sólido se recolectó por filtración y se secó para dar el compuesto deseado (**114**, 7.0 g).

*Etapa 2 – Preparación de 1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-carbaldehído (**115**):*

[0340] A 5-cloro-1H-pirrolo[2,3-b]piridin-3-carbaldehído (**114**, 3.60 g, 19.9 mmol) en 100 ml de diclorometano, hidróxido de potasio (50 ml, 9M acuoso, 0.45 mol), sulfato ácido de tetrabutilamonio (400 mg, 1.0 mmol) y cloruro de bencenosulfonilo (**11**, 2.9 ml, 23.0 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 3 horas, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se lavó con acetato de etilo para proporcionar el compuesto deseado como un sólido blanco (**115**, 2.3 g).

*Etapa 3 – Preparación de (1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[6-(2,2,5,5-tetrametil-[1,2,5]azadisilolidin-1-il)-piridin-3-il]-metanol (**118**) y (6-amino-piridin-3-il)-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**119**):*

[0341] En un matraz de fondo redondo, 2-amino-5-bromopiridina (**116**, 3.10 g, 17.9 mmol) se combinó con 80.0 ml de tetrahidrofurano bajo nitrógeno a -78 °C y n-butilitio (7.10 ml, 2.50 M en hexano, 17.8 mmol) se agregó lentamente. Después de 30 minutos, 1,2-bis-(cloro-dimetil-silanil)-etano (**117**, 3.90 g, 18.1 mmol) en 20 ml de tetrahidrofurano se agregó lentamente, y la reacción se

dejó llegar a temperatura ambiente durante una hora. La reacción se enfrió a -78 °C y n-butilitio adicional (7.10 ml, 2.50 M en hexano, 17.8 mmol) se agregó. La reacción se agitó durante 30 minutos a -78 °C y se dejó calentar a temperatura ambiente durante una hora. La reacción se enfrió a -78 °C y n-butilitio adicional (7.50 ml, 2.50 M en hexano, 18.8 mmol) se agregó lentamente. Después de 1 hora, 1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-carbaldehído (**115**, 1.90 g, 5.92 mmol) en 30 ml de tetrahidrofurano se agregó y la reacción se agitó a -78 °C durante 2 horas, luego se dejó calentar a temperatura ambiente durante 1 hora. La reacción se vertió en agua, se extrajo con acetato de etilo y la capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 2-20% de metanol en diclorometano para proporcionar un mezcla de compuestos (**118**, 1.7 g) y (**119**, 1.25 g). MS (ESI) $[M+H^+]^+$ = 554.4 para **118** y $[M-H^+]^-$ = 415.2 para **119**.

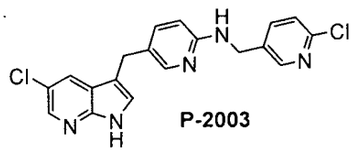
*Etapa 4 – Preparación de 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**120**):*

[0342] A (1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[6-(2,2,5,5-tetrametil-[1,2,5]azadisilolidin-1-il)-piridin-3-il]-metanol y (6-amino-piridin-3-il)-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**118**, **119**, 1.70/1.25 g mix, 2.41 mmol) en 25.0 ml de diclorometano, trietilsilano (3.00 ml, 18.8 mmol) y ácido trifluoroacético (1.50 ml, 19.5 mmol) se agregaron y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró bajo vacío, se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano para proporcionar el compuesto deseado (**120**, 0.70 g).

*Etapa 5 – Preparación de (6-bromo-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2002**):*

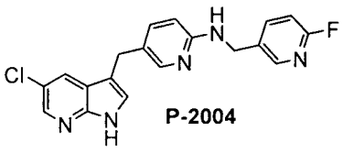
[0343] A 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**120**, 80.0 mg, 0.200 mmol) en 2.00 ml de etanol y 0.10 ml de ácido acético, 6-bromo-piridin-3-carbaldehído (**121**, 100.0 mg, 0.538 mmol) y cianoborohidruro soportado en sílice (0.50 g, 1.21 mmol/g) se agregaron. La reacción se calentó a 110 °C durante 25 minutos en horno de microondas. Hidróxido de sodio (2.0 ml, 6.0 M acuoso) se agregó y la reacción se calentó a 100 °C durante 10 minutos en horno de microondas, luego se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y el solvente se removió bajo vacío para proporcionar el compuesto deseado (**P-2002**, 26.6 mg). MS (ESI) $[M+H^+]^+$ = 427.7, 429.7.

[0344] (6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-2003**, y [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina **P-2004**,



P-2003

, y



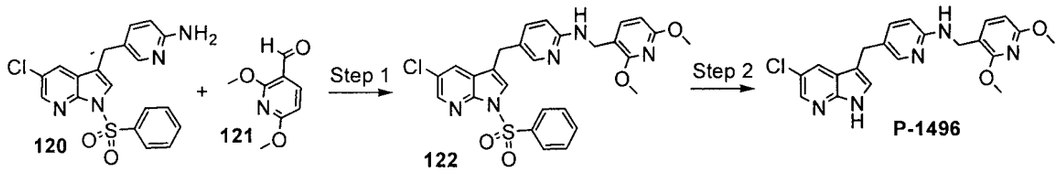
P-2004

se prepararon de manera similar al protocolo del Esquema 11, reemplazando 6-bromo-piridin-3-carbaldehído **121** con 6-cloro-piridin-3-carbaldehído y 6-fluoro-piridin-3-carbaldehído, respectivamente. MS (ESI) $[M+H^+]^+$ = 383.9, 385.9 (**P-2003**) y 367.9, 368.9 (**P-2004**).

Ejemplo 12: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina P-1496.

[0345] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina **P-1496** se preparó en dos etapas a partir de 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **120** y 2,6-dimetoxi-piridin-3-carbaldehído **121** como se muestra en el Esquema 12.

Esquema 12



Etapa 1 – Preparación de [5-(1-Bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (122):

[0346] A 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**120**, 60.0 mg, 0.150 mmol) en 2.0 ml de etanol y 0.1 ml de ácido acético, 2,6-dimetoxi-piridin-3-carbaldehído (**121**, 120 mg, 0.75 mmol) y cianoborohidruro soportado en sílice (0.40 g, 0.484 mmol) se agregaron. La reacción se calentó a 100 °C durante 18 minutos a 300 Watts en horno de microondas, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20 % de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**122**, 60 mg).

*Etapa 2 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-1496**):*

[0347] A [5-(1-Bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**122**, 60 mg, 0.11 mmol) en 10.0 ml de metanol, hidróxido de potasio (0.20 g, 3.6 mmol) se agregó. La reacción se agitó a 60 °C durante 4 horas, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**P-1496**, 26.1 mg). MS (ESI) $[M+H^+]^+ = 410.0$.

[0348] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 12, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Por ejemplo, sin limitación, fluoruro de tetrabutilamonio trihidratado se usa en lugar de hidróxido de potasio en la etapa 2. Los compuestos se preparan sustituyendo opcionalmente 2,6-dimetoxi-piridin-3-carbaldehído **121** con un aldehído adecuado y sustituyendo opcionalmente 5-(1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **120** con una 1H-pirrolo[2,3-b]piridina adecuada protegida con 1-bencenosulfonilo. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

(6-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1498**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1502**),

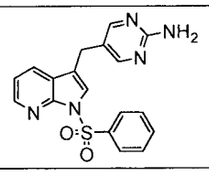
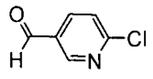
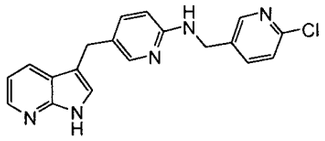
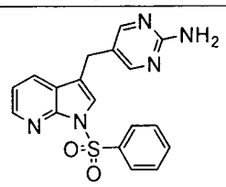
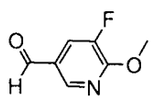
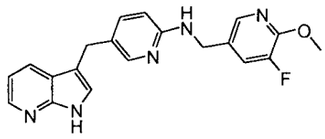
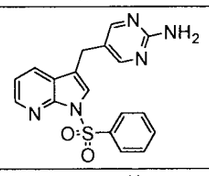
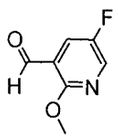
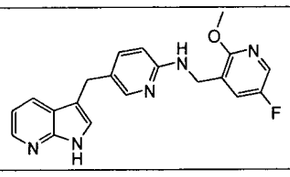
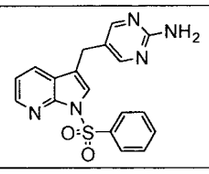
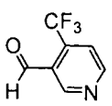
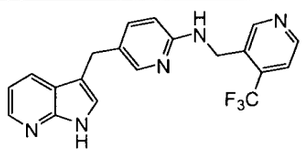
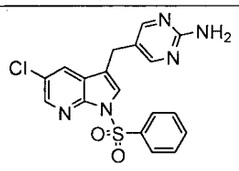
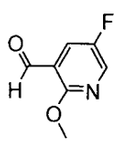
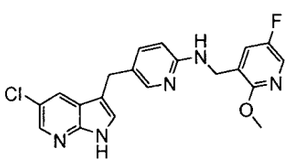
(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1503**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1504**), y

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1505**).

La siguiente tabla indica la 1H-pirrolo[2,3-b]piridina protegida con 1-bencenosulfonilo (columna 2) y

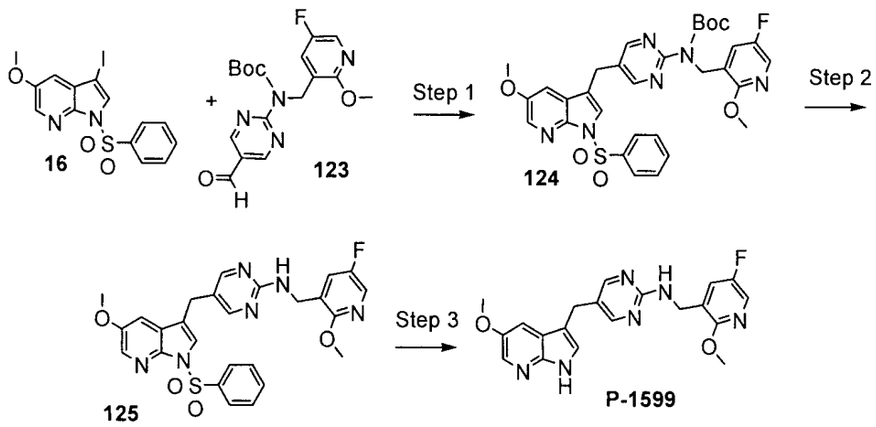
el compuesto aldehído (columna 3) usado en la etapa 1 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de comp.	1H-pirrolo[2,3-b]piridina	Estructura del aldehído	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-1498				
P-1502				
P-1503				
P-1504				
P-1505				

Ejemplo 13: Síntesis de (5-fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina P-1599.

[0349] (5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **P-1599** se prepara en tres etapas a partir de 1-bencenosulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina **16** y ter-butiléster del ácido (5-fluoro-2-metoxi-piridin-3-ilmetil)-(5-formil-pirimidin-2-il)-carbámico **123** como se muestra en el Esquema 13.

Esquema 13



*Etapa 1 – Preparación de ter-butiléster del ácido {5-[(1-bencenosulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-pirimidin-2-il}-(5-fluoro-2-metoxi-piridin-3-ilmetil)-carbámico (**124**):*

[0350] A una solución de 1-bencenosulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina (**16**, 1 equivalente) en 4.0 ml de tetrahidrofurano, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 1 equivalente) se agrega lentamente a -50 °C. La reacción se dejó calentar a 5 °C durante 70 minutos, luego se enfrió a -45 °C y ter-butiléster del ácido (5-fluoro-2-metoxi-piridin-3-ilmetil)-(5-formil-pirimidin-2-il)-carbámico (**123**, 0.78 equivalente) en 2.0 ml de tetrahidrofurano se agregó. La reacción se dejó calentar a temperatura ambiente durante 1 hora, luego se vertió en cloruro de amonio acuoso y se extrajo con etil éter. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

*Etapa 2 – Preparación de [5-(1-bencenosulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**125**):*

[0351] A ter-butiléster del ácido {5-[(1-bencenosulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-pirimidin-2-il}-(5-fluoro-2-metoxi-piridin-3-ilmetil)-carbámico (**124**, 1 equivalente) en 10.0 ml de acetonitrilo, trietilsilano (15.6 equivalentes) y ácido trifluoroacético (16.9 equivalentes) se agregan. La reacción se calentó a 80 °C durante 2 horas, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado, el cual se usa en la siguiente etapa sin purificación adicional.

*Etapa 3 – Preparación de (5-fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1599**):*

[0352] A [5-(1-bencenosulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**125**, 1 equivalente) en 15.0 ml de tetrahidrofurano, fluoruro

de tetrabutilamonio trihidratado (2 equivalente) se agrega. La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado como un sólido amarillo.

[0353] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 13, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan usando un aldehído adecuado protegido con Boc en lugar de ter-butiléster del ácido (5-fluoro-2-metoxi-piridin-3-ilmetil)-(5-formil-pirimidin-2-il)-carbámico **123** en la etapa 1. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1600**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1601**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1602**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1603**),

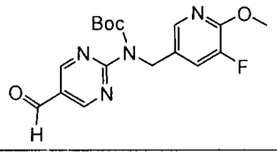
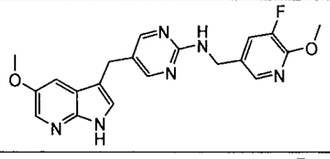
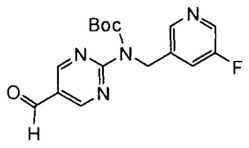
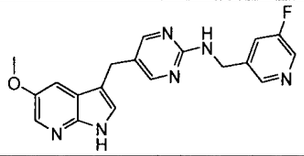
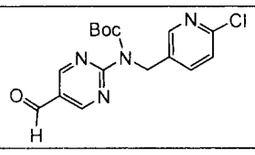
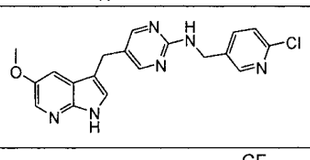
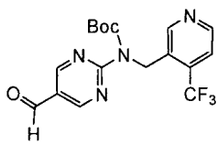
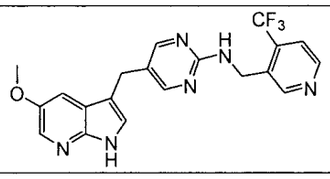
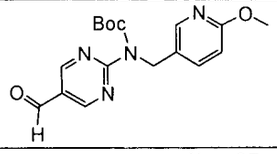
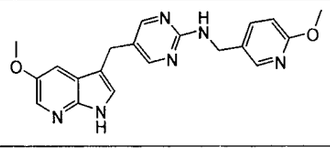
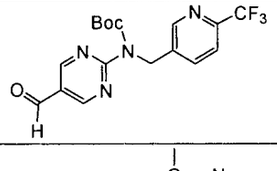
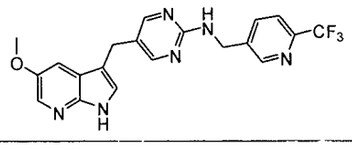
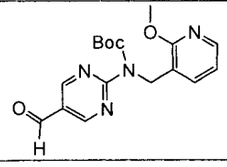
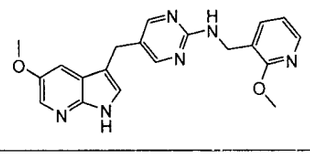
(6-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1604**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1605**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1606**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina (**P-2203**), y

3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204)**.

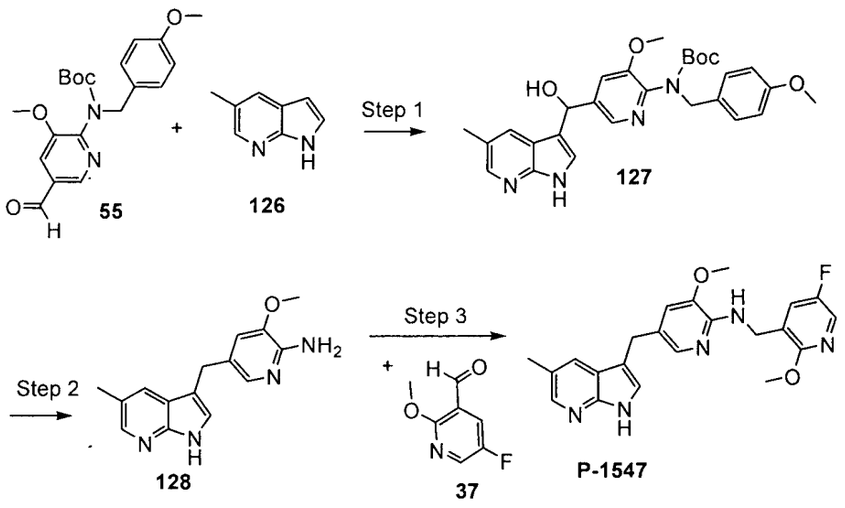
La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 1 para proporcionar el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

Número de compuesto	Aldehído	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-1600			
P-1601			
P-1602			
P-1603			
P-1604			
P-1605			
P-1606			

Ejemplo 14: Síntesis de (5-fluoro-2-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-1547.

[0354] (5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-1547** se prepara en tres etapas a partir de ter-butiléster del ácido (5-formil-3-metoxi-piridin-2-il)-(4-metoxi-bencil)-carbámico **55** y 5-metil-1H-[2,3-b]piridina **126** como se muestra en el Esquema 14.

Esquema 14



Etapa 1 – Preparación de ter-butiléster del ácido {5-[hidroxi-(5-metil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-3-metoxi-piridin-2-il}-(4-metoxi-bencil)-carbámico (127):

[0355] En un vial, 5-metil-1H-[2,3-b]piridina (**126**, 1 equivalente) se combinó con ter-butiléster del ácido (5-formil-3-metoxi-piridin-2-il)-(4-metoxi-bencil)-carbámico (**55**, 1.1 equivalentes), 5 ml de metanol, e hidróxido de potasio (3 equivalentes). La reacción se agitó a temperatura ambiente durante la noche, luego ácido clorhídrico acuoso 1N se agrega y la mezcla se extrae con acetato de etilo. La capa orgánica se lavó con agua, salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

Etapa 2 – Preparación de 3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (128):

[0356] En un matraz de fondo redondo, ter-butiléster del ácido {5-[hidroxi-(5-metil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-3-metoxi-piridin-2-il}-(4-metoxi-bencil)-carbámico (**127**, 1 equivalente) se combinó con 100 ml de acetonitrilo, trietilsilano (18 equivalentes), y ácido trifluoroacético (18 equivalentes). La reacción se calentó a reflujo durante 24 horas, luego se concentró bajo vacío. El material resultante se disolvió en 40 ml de ácido trifluoroacético y se agitó a temperatura ambiente durante 18 horas. Este se concentró bajo vacío y se combinó con agua y bicarbonato de sodio, luego se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato de sodio, agua, salmuera,

luego se secó con sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

*Etapa 3 – Preparación de (5-fluoro-2-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1547**):*

[0357] A 3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**128**, 1 equivalente) en 2 ml de acetonitrilo, 5-fluoro-2-metoxi-piridin-3-carbaldehído (**37**, 1 equivalente), trietilsilano (5 equivalentes) y ácido trifluoroacético (6.9 equivalentes) se agregan. La reacción se calentó a 80 °C durante 18 horas, luego se concentró bajo vacío y se mezcló con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con agua, salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

[0358] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 14, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan usando un aldehído adecuado en lugar de 5-fluoro-2-metoxi-piridin-3-carbaldehído **37 en la etapa** 3. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1548**),

(5-Fluoro-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1549**),

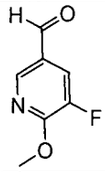
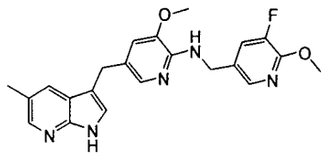
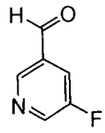
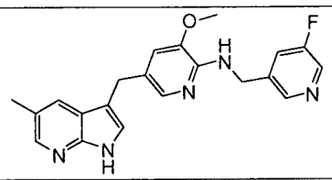
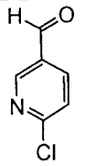
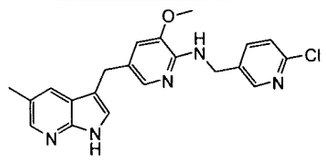
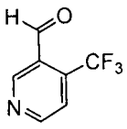
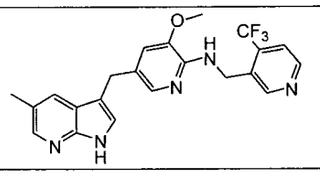
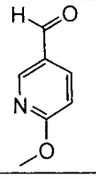
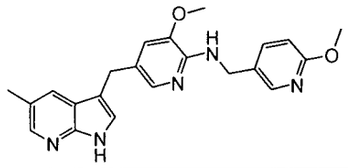
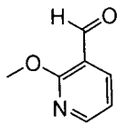
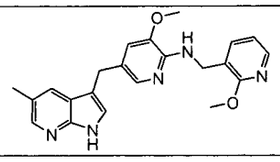
(6-Cloro-piridin-3-ilmetil)-[3-metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1550**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1551**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1552**), y

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1553**).

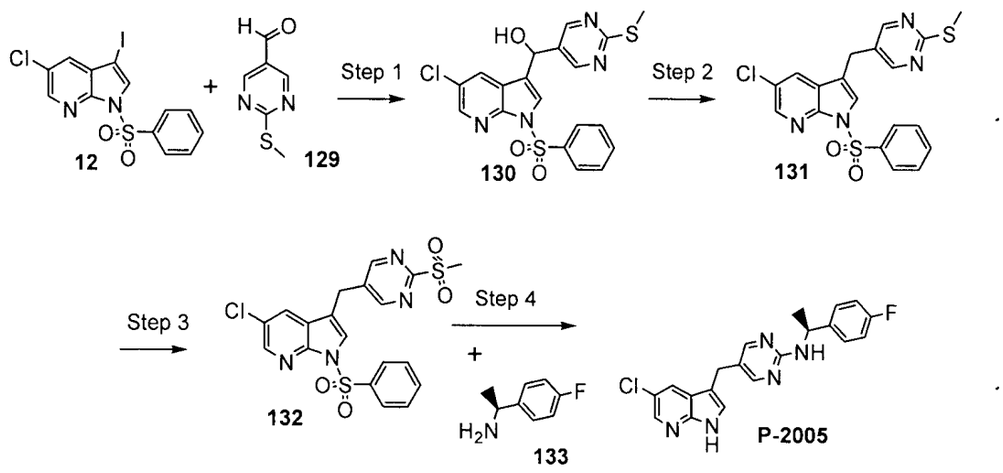
La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 3 para proporcionar el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

Número de compuesto	Aldehído	Compuesto	MS (ESI) $[M+H^+]^+$
P-1548			
P-1549			
P-1550			
P-1551			
P-1552			
P-1553			

Ejemplo 15: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina P-2005.

[0359] [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina **P-2005** se preparó en 4 etapas a partir de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **12** y 2-metilsulfanil-pirimidin-5-carbaldehído **129** como se muestra en el Esquema 15.

Esquema 15



*Etapa 1 – Preparación de (1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**130**):*

[0360] A una solución de 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**12**, 8.40 g, 20.1 mmol) en 96.3 ml de tetrahidrofurano a -40 °C bajo nitrógeno, cloruro de isopropilmagnesio (10.1 ml, 2.0 M en tetrahidrofurano, 20.3 mmol) se agregó lentamente. La reacción se dejó calentar a 5 °C durante 60 minutos, luego se enfrió a -40 °C, seguido por adición de 2-metilsulfanil-pirimidin-5-carbaldehído (**129**, 2.50 g, 16.2 mmol) en 15.0 ml de tetrahidrofurano. La reacción se dejó calentar a 10 °C durante 2 horas, luego se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 40-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado como un sólido blanquecino (**130**, 4.0 g). MS (ESI) $[M+H^+]^+ = 447.2$.

*Etapa 2 – Preparación de 1-bencenosulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**131**):*

[0361] A (1-bencenosulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**130**, 4.70 g, 10.5 mmol) en 120.0 ml de acetonitrilo, trietilsilano (22.0 ml, 138 mmol) y ácido trifluoroacético (11.0 ml, 143 mmol) se agregaron. La reacción se agitó a 80 °C durante 3 horas, luego se concentró bajo vacío y se mezcló con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró

bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**131**, 2.90 g).

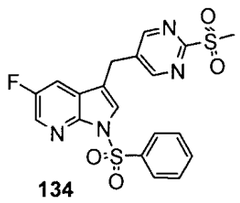
*Etapa 3 – Preparación de 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**132**):*

[0362] A 1-bencenosulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**131**, 4.40 g, 10.2 mmol) en 100.0 ml de diclorometano, ácido meta-cloroperoxibenzoico (máx. 77%, 4.90 g, 21.9 mmol) se agregó a 0 °C. La reacción se agitó a 0 °C durante 40 minutos, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró, y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**132**, 3.76 g). MS (ESI) $[M+H^+]^+ = 463.0$.

*Etapa 4 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina (**P-2005**):*

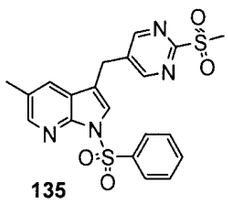
[0363] En un vial para horno de microondas, 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**132**, 12 mg, 0.026 mmol) se mezcló con 600 µL de N-metilpirrolidinona y (S)-1-(4-fluoro-fenil)-etilamina (**133**, 25.2 mg, 0.18 mmol). La reacción se irradió a 200 °C durante 40 minutos en horno de microondas, luego hidróxido de potasio (500 µL, 4.00 M en agua) se agregó y la reacción se irradió a 90 °C durante 10 minutos en horno de microondas. La reacción se neutralizó con la adición de 120 µL de ácido acético, los solventes se removieron bajo vacío, y el material resultante se disolvió en 400 µL de sulfóxido de dimetilo para purificación por HPLC. El compuesto deseado se purificó en columna Fenomenex C18 (50 mm x 10 mm ID) con fase móvil A de 0.1% de ácido trifluoroacético en agua, fase móvil B de 0.1% de ácido trifluoroacético en acetonitrilo, 20-100% B durante 16 minutos a un flujo volumétrico de 6 ml/min. Las fracciones apropiadas se recolectaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 381.9$.

[0364] · 1-Bencenosulfonil-5-fluoro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **134** y 1-bencenosulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-5-metil-1H-pirrolo[2,3-b]piridina **135**



134

y



135

se preparan de manera similar siguiendo el protocolo del Esquema 15, etapas 1-3, reemplazando 1-bencenosulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **12** con 1-bencenosulfonil-5-fluoro-3-yodo-1H-pirrolo[2,3-b]piridina o 1-bencenosulfonil-3-yodo-5-metil-1H-pirrolo[2,3-b]piridina respectivamente en la etapa 1. Estos se usan siguiendo el protocolo del Esquema 15 etapa 4 para elaborar compuestos adicionales. En algunos casos para los compuestos 5-fluoro sustituidos, la remoción del grupo protector bencenosulfonilo se hace en una etapa adicional al hacerse reaccionar con fluoruro de tetrabutilamonio trihidratado en tetrahidrofurano.

[0365] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 15, etapa 4, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan sustituyendo (S)-1-(4-fluoro-fenil)-etilamina **133** con una amina adecuada y sustituyendo opcionalmente 1-bencenosulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **132** con 1-bencenosulfonil-5-fluoro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **134** o 1-bencenosulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-5-metil-1H-pirrolo[2,3-b]piridina **135**. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

(3-Cloro-4-metil-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2007**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3,4-difluoro-bencil)-amina (**P-2008**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-5-trifluorometil-bencil)-amina (**P-2009**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometoxi-bencil)-amina (**P-2010**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-4-trifluorometil-bencil)-

amina (**P-2011**),

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-metil-amina (**P-2012**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-metil-bencil)-amina (**P-2013**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-4-metil-bencil)-amina (**P-2014**),

[2-(3-Cloro-fenil)-etil]-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2015**),

[2-(2-Cloro-fenil)-etil]-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2020**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[2-(4-fluoro-fenil)-etil]-amina (**P-2021**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-[2-(6-metil-piridin-2-il)-etil]-amina (**P-2022**),

Butil-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2026**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(1-tiazol-2-il-etil)-amina (**P-2039**),

[1-(4-Fluoro-fenil)-propil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2053**),

[1-(4-Fluoro-fenil)-ciclopropil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2055**),

[(S)-1-(4-Fluoro-fenil)-etil]-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2056**),

(2-Metoxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2069**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-4-ilmetil)-amina (**P-2074**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-2-ilmetil-amina (**P-2076**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-3-ilmetil-amina (**P-2077**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina

(**P-2078**),

(6-Metil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2079**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2080**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina (**P-2081**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2082**),

(5-Etil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2083**),

(3-Metil-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2084**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-morfolin-4-il-piridin-4-ilmetil)-amina (**P-2085**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-piridin-4-ilmetil-amina (**P-2138**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2139**),

[6-(4-Metil-piperazin-1-il)-piridin-3-ilmetil]-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2140**),

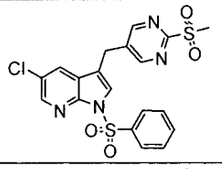
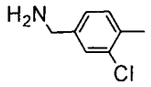
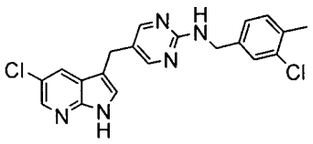
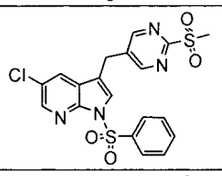
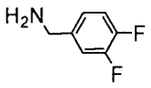
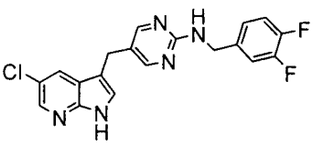
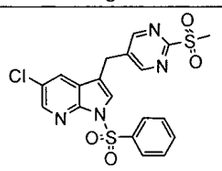
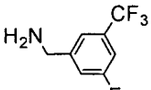
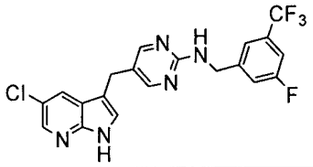
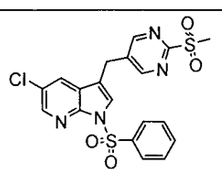
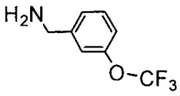
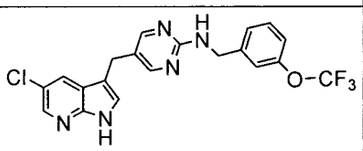
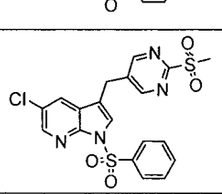
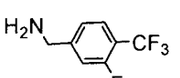
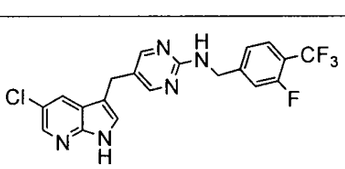
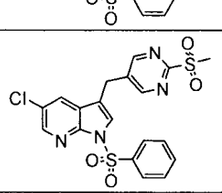
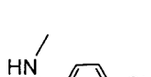
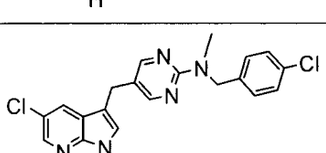
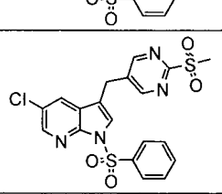
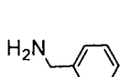
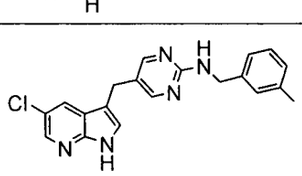
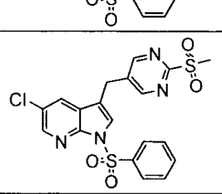
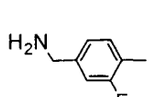
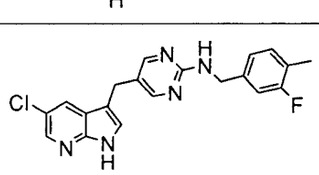
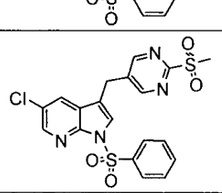
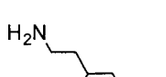
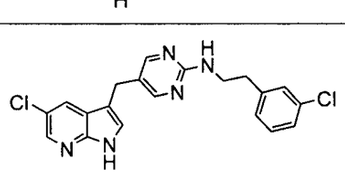
(2-Metil-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2141**),

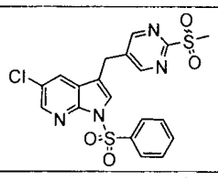
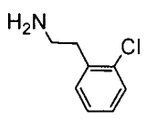
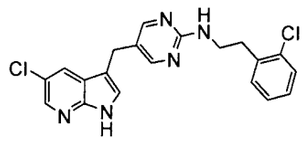
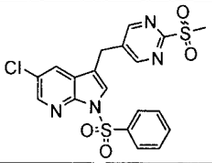
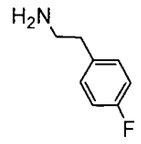
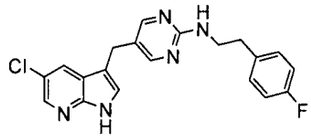
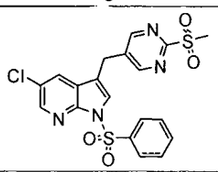
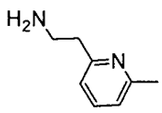
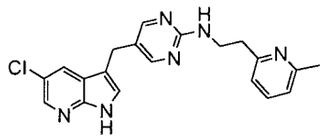
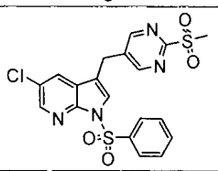
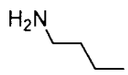
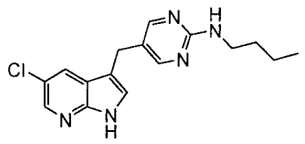
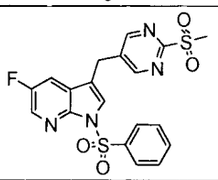
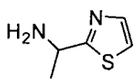
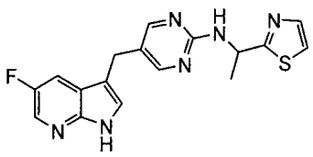
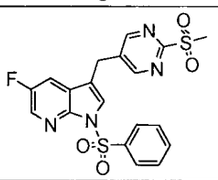
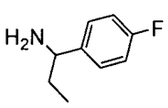
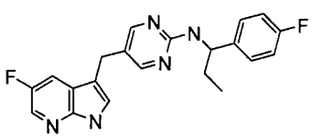
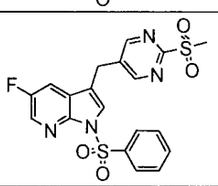
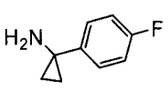
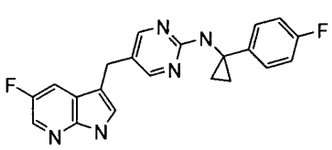
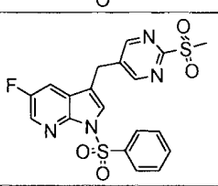
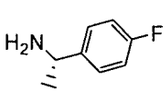
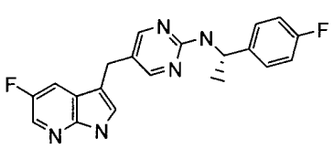
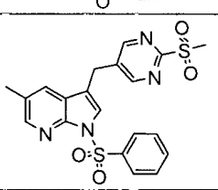
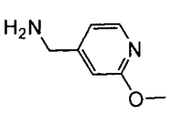
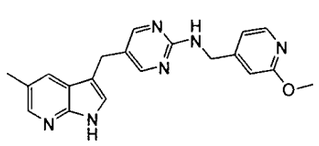
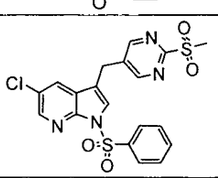
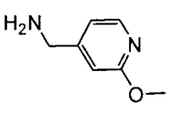
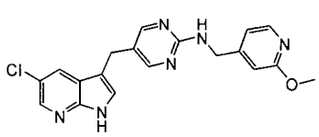
(2-Etoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2142**),

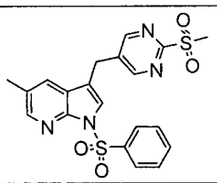
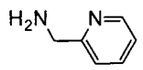
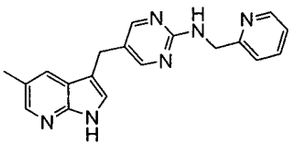
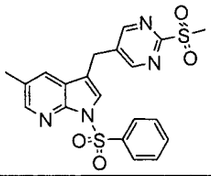
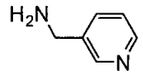
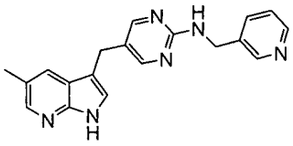
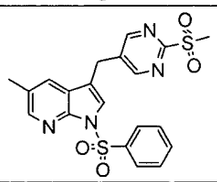
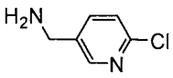
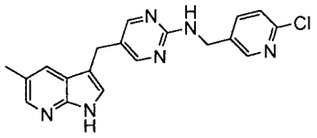
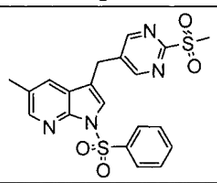
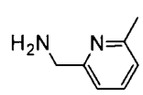
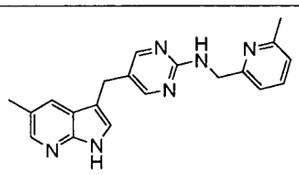
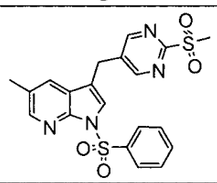
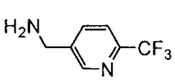
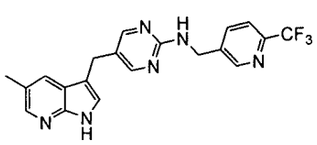
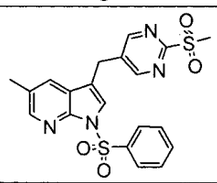
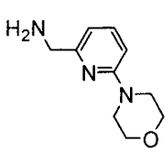
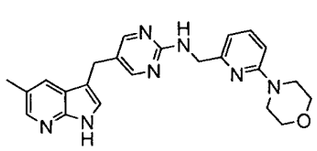
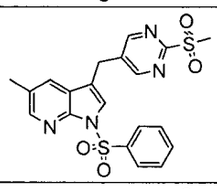
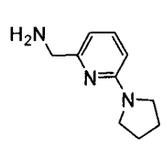
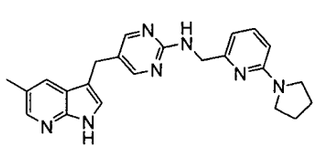
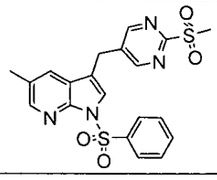
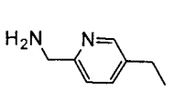
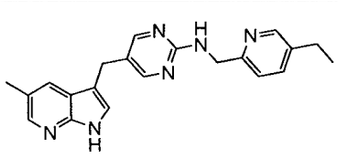
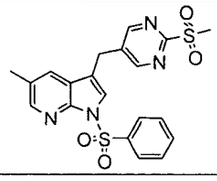
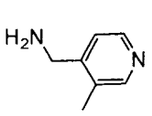
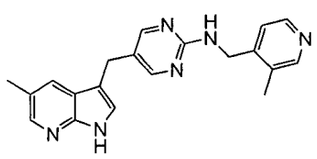
(2-Ciclopentiloxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2148**), y

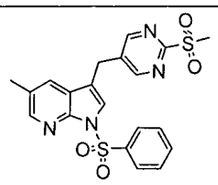
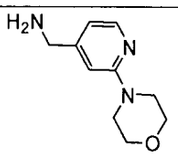
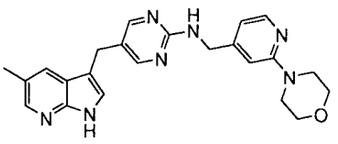
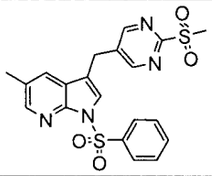
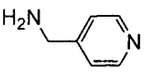
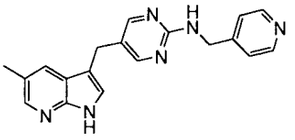
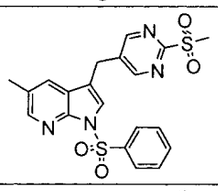
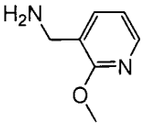
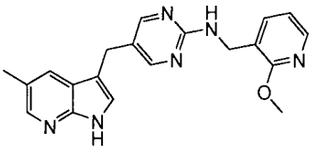
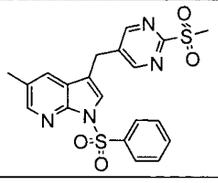
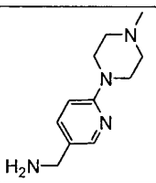
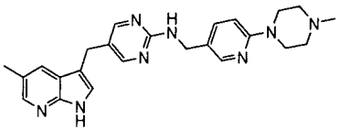
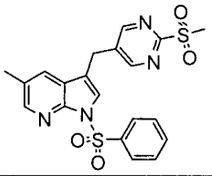
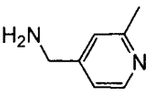
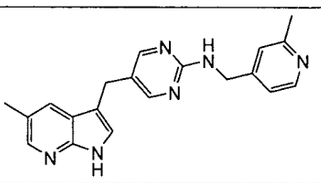
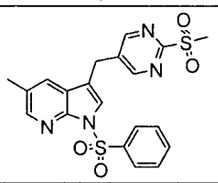
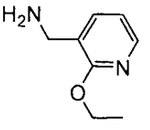
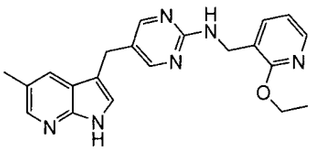
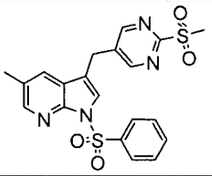
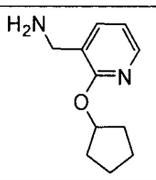
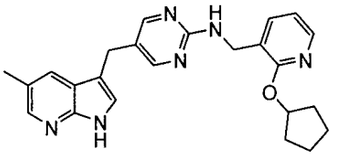
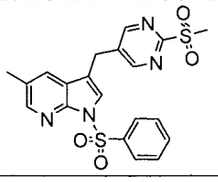
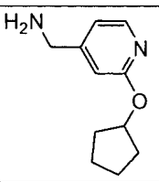
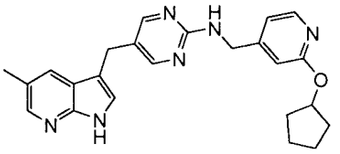
(2-Ciclopentiloxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2149**).

La siguiente tabla indica la 1H-pirrolo[2,3-b]piridina (columna 2) y el compuesto amina (columna 3) usado en la etapa 4 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de comp.	1H-pirrolo[2,3-b]piridina	Estructura de la amina	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
P-2007				397.9
P-2008				386.3
P-2009				436.3
P-2010				434.3
P-2011				435.9
P-2012				
P-2013				364.3
P-2014				381.9
P-2015				397.9

P-2020				397.9 399.95
P-2021				384.0
P-2022				379.4
P-2026				
P-2039				
P-2053				
P-2055				377.9
P-2056				366.0
P-2069				
P-2074				380.9

P-2076				
P-2077				
P-2078				365.1
P-2079				345.1
P-2080				
P-2081				416.3
P-2082				400.3
P-2083				
P-2084				

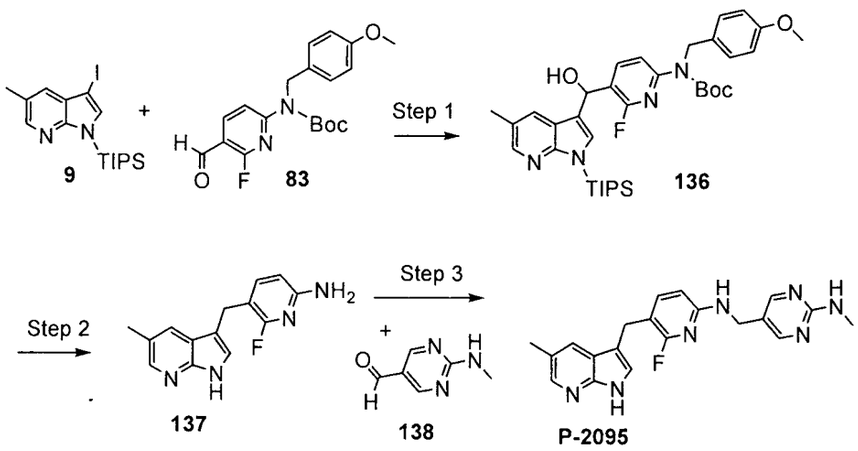
P-2085				
P-2138				
P-2139				361.5
P-2140				
P-2141				
P-2142				
P-2148				415.5
P-2149				

Ejemplo 16: Síntesis de (5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-metil-amina P-2095.

[0366] (5-{[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-metil-amina **P-2095** se preparó en tres etapas a partir de 3-yodo-5-metil-1-

triisopropilsilanil-1H-pirrolo[2,3-b]piridina **9** y ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico **83** como se muestra en el Esquema 16.

Esquema 16



*Etapa 1 – Preparación de ter-butiléster del ácido {6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il}-(4-metoxi-bencil)-carbámico (**136**):*

[0367] A 3-yodo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**9**, 40 g, 97.0 mmol) en 400 ml de tetrahidrofurano bajo nitrógeno a -20 °C, cloruro de isopropilmagnesio (54.8 ml, 2 M en tetrahidrofurano, 110 mmol) se agregó y la reacción se dejó calentar a 0 °C durante 30 minutos. La reacción se enfrió a -40 °C y ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico (**83**, 15.81 g, 43.9 mmol) en tetrahidrofurano se agregó. La reacción se dejó calentar a 0 °C durante una hora, luego se extinguió con salmuera y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-40% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**136**, 21 g, 32.4 mmol, 73.8 % de rendimiento).

Etapa 2 – Preparación de 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (137):

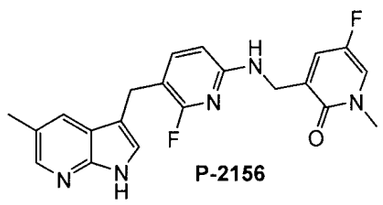
[0368] A ter-butiléster del ácido {6-fluoro-5-[hidroxi-(5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il}-(4-metoxi-bencil)-carbámico (**136**, 21 g, 32.4 mmol) en 500 ml de acetonitrilo, trietilsilano (51.7 ml, 324 mmol) y ácido trifluoroacético (24.93 ml, 324 mmol) se agregaron. La reacción se agitó a 50 °C durante varias horas, los solventes se removieron bajo vacío, y el residuo se recogió en 250 ml de diclorometano y 250 ml de ácido trifluoroacético se agregaron. La mezcla se agitó a reflujo durante varias horas, luego se concentró bajo vacío. El residuo se recogió en acetato de etilo y se vertió en carbonato de potasio acuoso. La capa orgánica se separó, se

concentró bajo vacío y se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-5% de metanol en diclorometano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado (**137**, 5.2 g, 20.29 mmol, 62.7 % de rendimiento).

*Etapa 3 – Preparación de (5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-metil-amina (**P-2095**):*

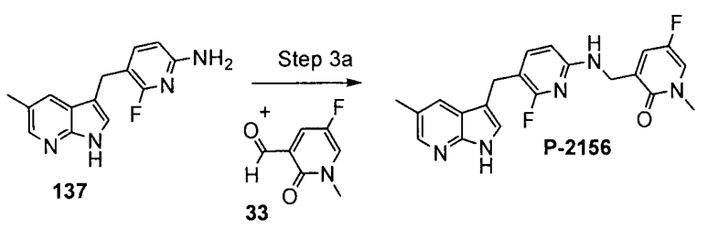
[0369] En un vial de 2 ml para horno de microondas, 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**137**, 9.72 mg, 0.04 mmol) y 2-metilamino-pirimidin-5-carbaldehído (**138**, 11.0 mg, 0.08 mmol) se disolvieron en 600 µL de 95:5 etanol:ácido acético, y cianoborohidruro soportado en sílice (50 mg, 1mmol/g, 0.05 mmol) se agregó. La reacción se irradió durante 10 minutos a 160 °C en un horno de microondas. El vial se centrifugó para condensar la sílice y el sobrenadante se removió por pipeta a otro vial. La sílice residual se enjuagó con 500 µL de etanol, se centrifugó y el sobrenadante se agregó al primer sobrenadante. Los solventes se removieron bajo vacío y el material resultante se disolvió en 400 µL de sulfóxido de dimetilo para purificación por HPLC. Las muestras se purificaron en columna Fenomenex C18 (50 mm x 10 mm ID) con fase móvil A de 0.1% de ácido trifluoroacético en agua, fase móvil B de 0.1% de ácido trifluoroacético en acetonitrilo, 20-100% B durante 16 minutos a un flujo volumétrico de 6 ml/min. Las fracciones apropiadas se recolectaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 378.3$.

[0370] 5-Fluoro-3-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-1-metil-1H-piridin-2-ona **P-2156**



P-2156

se preparó de manera similar al protocolo del Esquema 16, donde la etapa 3 se reemplazó por la siguiente etapa 3a:

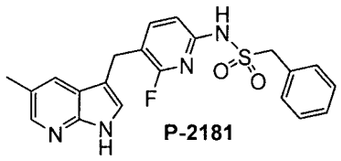


137 **33** **P-2156**

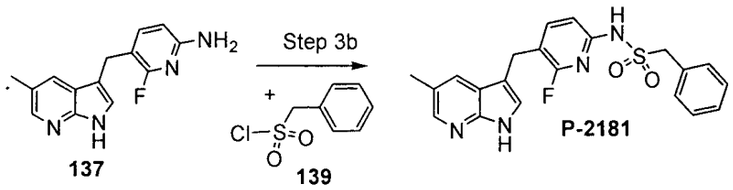
*Etapa 3a – Preparación de 5-fluoro-3-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-1-metil-1H-piridin-2-ona (**P-2156**):*

[0371] A 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**137**, 3.99 g, 15.59 mmol) y 5-fluoro-1-metil-2-oxo-1,2-dihidro-piridin-3-carbaldehído (**33**, 2.66 g, 17.15 mmol) en 50 ml de acetonitrilo, trietilsilano (9.96 ml, 62.4 mmol) y ácido trifluoroacético (4.80 ml, 62.4 mmol) se agregaron. La reacción se agitó a 80 °C durante varias horas, luego se concentró bajo vacío y el residuo se recogió en acetato de etilo y se vertió en carbonato de potasio acuoso. La capa orgánica se separó, se concentró bajo vacío, y el residuo se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-5% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío, y el residuo se trituró con metanol para proporcionar el compuesto deseado (**P-2156**, 3.1 g, 7.84 mmol, 50.3 % de rendimiento).

[0372] N-[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-C-fenil-metanosulfonamida **P-2181**



de manera similar al protocolo del Esquema 16, donde la etapa 3 se reemplazó por la siguiente etapa 3b:



*Etapa 3b – Preparación de N-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-C-fenil-metanosulfonamida (**P-2181**):*

[0373] . En un vial, 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**137**, 157 mg, 0.614 mmol) se mezcló con 4 ml de diclorometano y piridina (149 µL, 1.84 mmol) y se enfrió a 0 °C en un baño de agua helada. Cloruro de fenil-metanosulfonilo (**139**, 0.234 g, 1.23 mmol) se agregó y la reacción se agitó a 0 °C durante 1 hora, luego se calentó a temperatura ambiente y se agitó durante la noche. Bicarbonato de sodio saturado acuoso se agregó y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-10% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**P-2181**, 39 mg). MS (ESI) $[M+H^+]^+$ = 411.1.

[0374] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 16 (etapa 3a puede sustituirse por la etapa 3) donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan sustituyendo opcionalmente 3-yódo-5-metil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **9** con una 1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina adecuada en la etapa 1; reemplazando opcionalmente ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico **83** con ter-butiléster del ácido (5-formil-pirimidin-2-il)-(4-metoxi-bencil)-carbámico en la etapa 1; y reemplazando opcionalmente 2-metilamino-pirimidin-5-carbaldehído **138** con un aldehído adecuado en la etapa 3. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1569**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1570**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1611**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1612**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1613**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1614**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1646**),

(5-Fluoro-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1647**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1648**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1649**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1650**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1651**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1652**),

[6-Fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1653**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2064**),

(2,5-Dimetoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2086**),

(3,5-Dimetoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2087**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2088**),

(3-Bromo-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2089**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-morfolin-4-il-piridin-3-ilmetil)-amina (**P-2090**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-morfolin-4-il-piridin-3-ilmetil)-amina (**P-2091**),

(3-Cloro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2092**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-2-ilmetil)-amina (**P-2093**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-fluoro-piridin-4-ilmetil)-amina (**P-2094**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina (**P-2096**),

(2,6-Dimetoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2097**),

(5-Fluoro-2-metanosulfonil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2098**),

(5-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2099**),

(5-Bromo-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2100**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-metil-piridin-4-ilmetil)-amina (**P-2101**),

(3-Cloro-5-fluoro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2102**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-3-ilmetil)-amina (**P-2103**),

(3,5-Dimetil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2104**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metoxi-piridin-3-ilmetil)-amina (**P-2105**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-pirimidin-5-ilmetil)-amina (**P-2106**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metilamino-piridin-3-ilmetil)-amina (**P-2107**),

(3,5-Bis-trifluorometil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2108**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-metoxi-piridin-3-ilmetil)-amina (**P-2109**),

(2-Etoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2110**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-isopropoxi-piridin-3-ilmetil)-amina (**P-2111**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-metil-piridin-2-ilmetil)-amina (**P-2112**),

(2-Ciclopentiloxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2113**),

(2-Ciclohexiloxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2114**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-piridin-3-ilmetil)-amina (**P-2115**),

(2-Cloro-5-fluoro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2116**),

4-{[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-carbonitrilo (**P-2117**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-4-ilmetil)-amina (**P-2118**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-piridin-4-ilmetil)-amina (**P-2119**),

(2-Cloro-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2120**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-morfolin-4-il-piridin-4-ilmetil)-amina (**P-2121**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-pirrolidin-1-il-piridin-4-ilmetil)-amina (**P-2122**),

(5-Cloro-2-fluoro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2123**),

(4-Cloro-2-metanosulfonil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2124**),

(2-Dimetilamino-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2125**),

(2-Etil-pirimidin-5-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2126**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-propil-pirimidin-5-ilmetil)-amina (**P-2127**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-isopropil-pirimidin-5-ilmetil)-amina (**P-2128**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2-metoxi-etil)-pirimidin-5-ilmetil]-amina (**P-2129**),

(2-Butil-pirimidin-5-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2130**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metil-piridin-2-ilmetil)-amina (**P-2131**),

(3-Fluoro-5-metil-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2132**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3-metoxi-5-trifluorometil-bencil)-amina (**P-2133**),

(3-Fluoro-5-metoxi-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2134**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(3,4,5-trimetoxi-bencil)-amina (**P-2150**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2151**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-6-trifluorometil-piridin-3-ilmetil)-amina (**P-2166**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-dimetilamino-6-trifluorometil-piridin-3-ilmetil)-amina (**P-2167**),

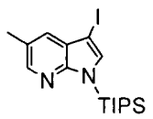
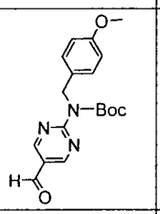
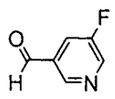
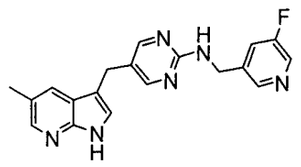
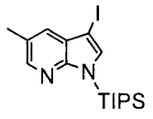
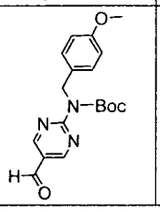
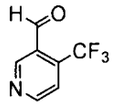
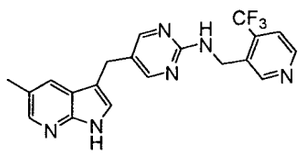
[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-4-trifluorometil-piridin-3-ilmetil)-amina (**P-2186**),

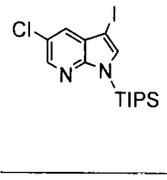
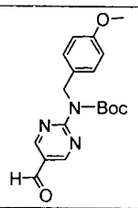
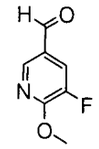
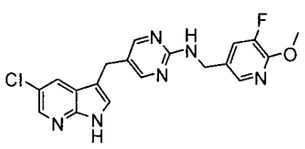
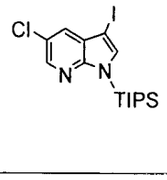
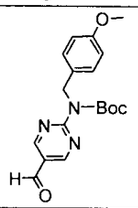
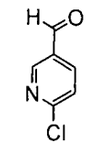
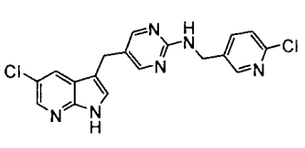
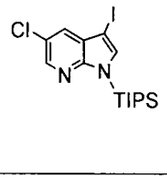
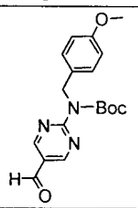
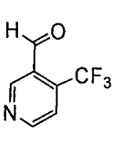
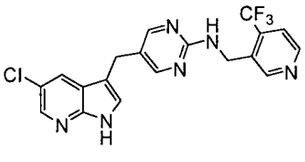
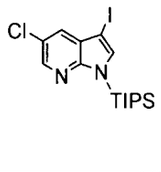
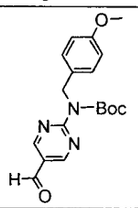
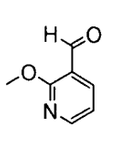
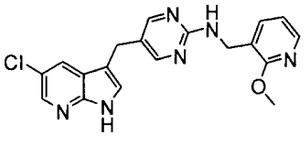
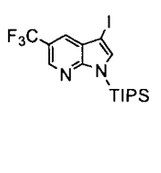
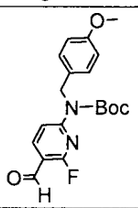
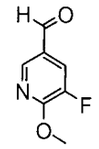
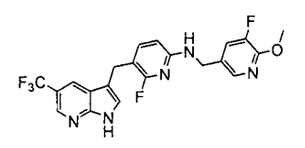
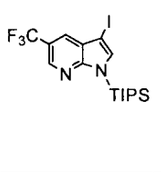
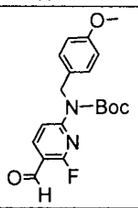
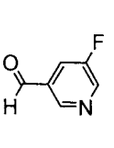
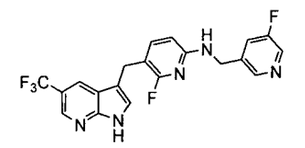
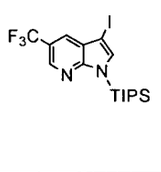
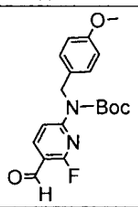
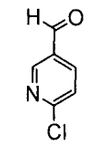
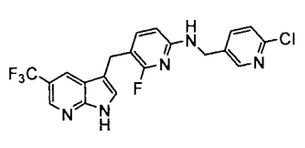
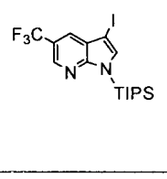
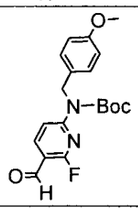
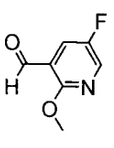
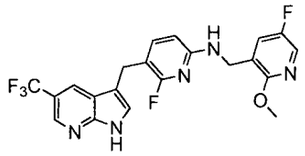
(2-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2198**),

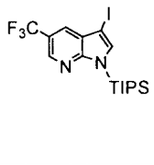
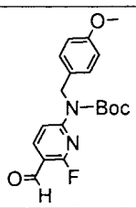
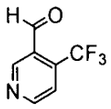
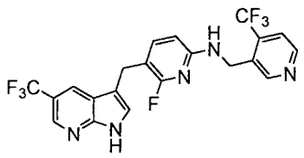
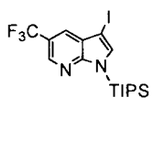
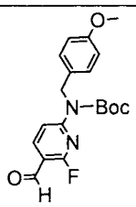
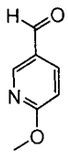
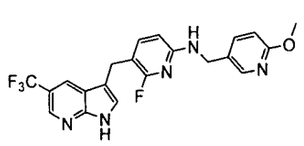
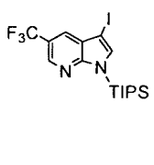
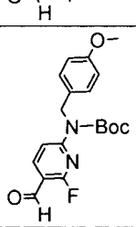
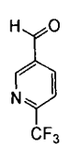
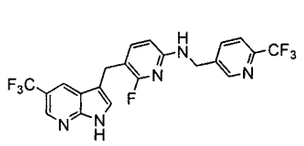
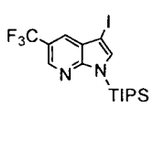
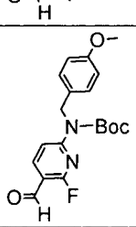
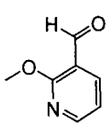
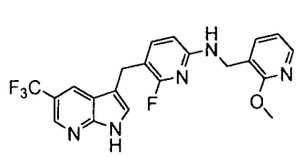
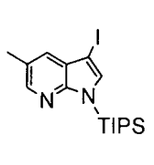
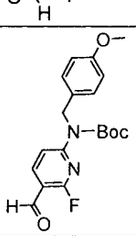
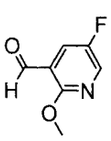
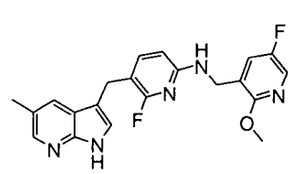
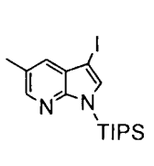
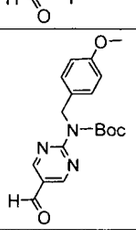
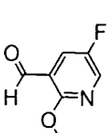
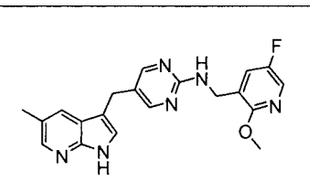
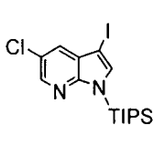
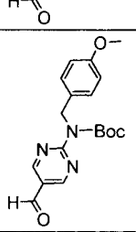
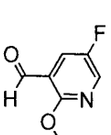
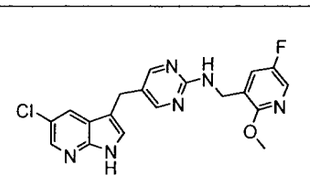
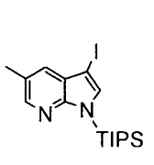
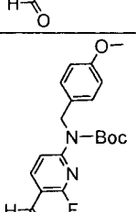
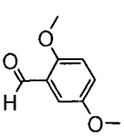
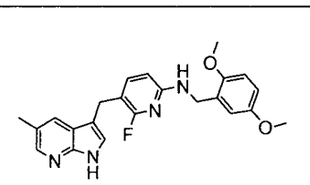
(4-fluoro-3-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2199**), y

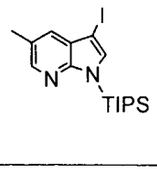
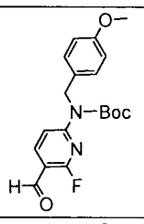
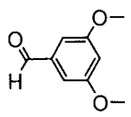
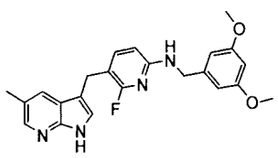
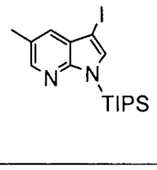
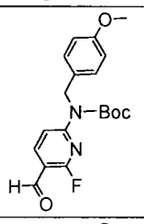
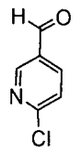
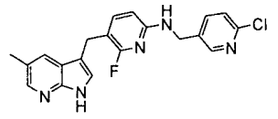
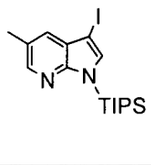
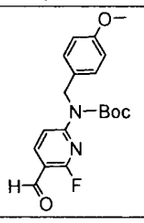
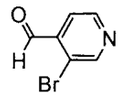
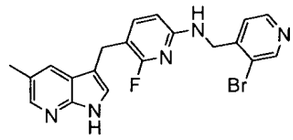
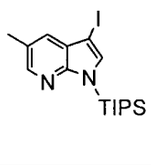
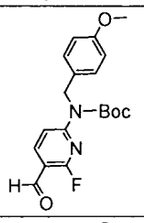
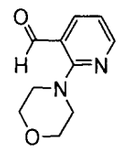
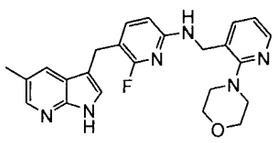
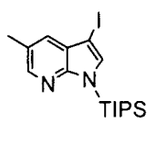
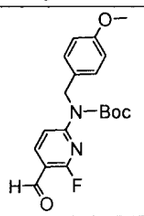
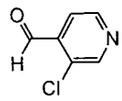
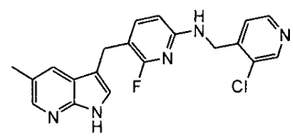
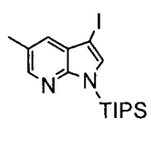
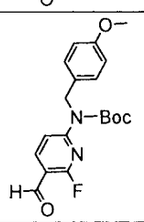
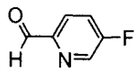
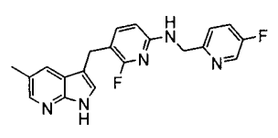
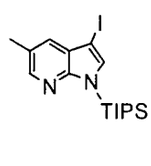
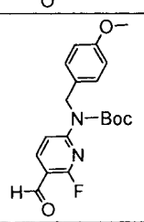
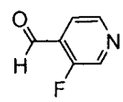
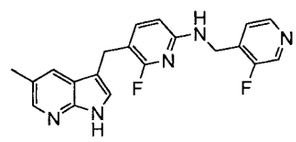
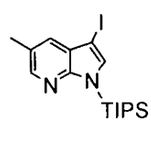
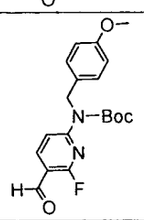
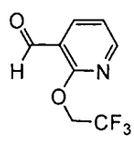
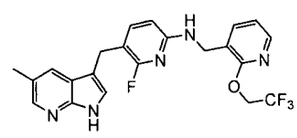
(3-fluoro-5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2202**).

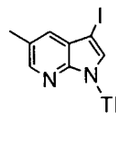
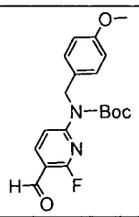
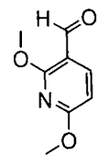
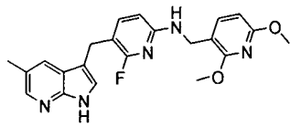
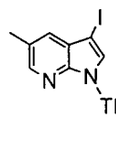
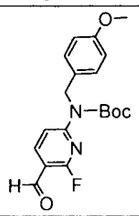
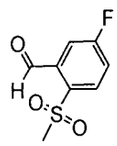
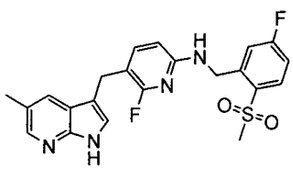
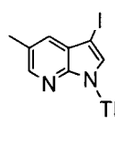
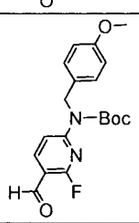
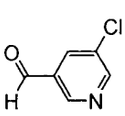
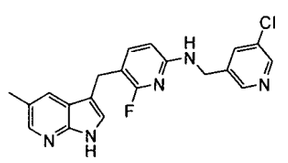
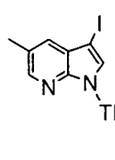
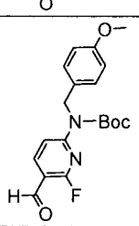
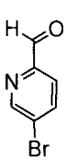
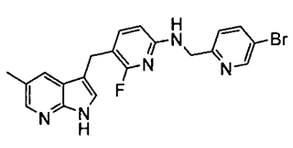
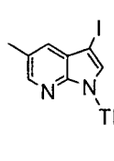
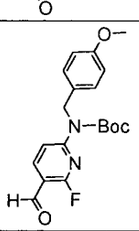
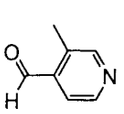
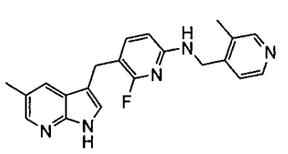
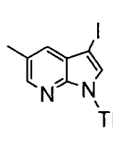
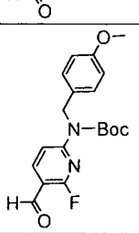
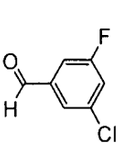
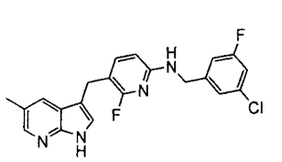
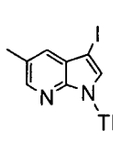
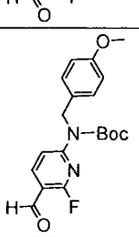
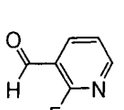
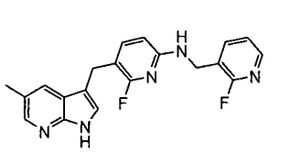
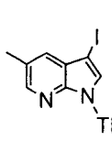
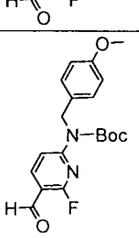
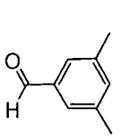
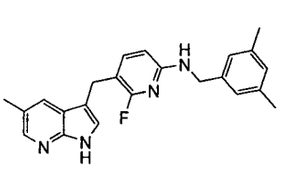
La siguiente tabla indica la 1H-pirrolo[2,3-b]piridina (columna 2) y Aldehído protegido con Boc (columna 3) usado en la etapa 1, y el compuesto aldehído (columna 4) usado en la etapa 3 (o 3a si se indica en la columna 1) para proporcionar el compuesto deseado (columna 5). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 6.

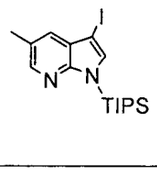
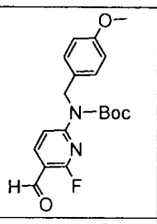
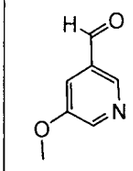
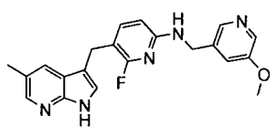
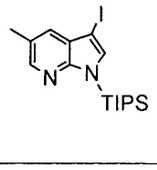
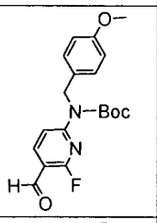
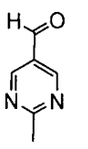
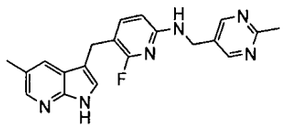
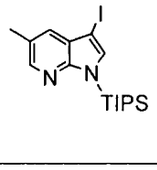
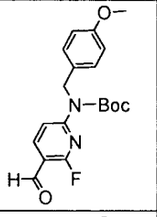
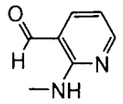
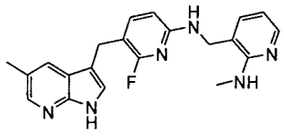
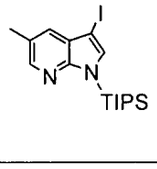
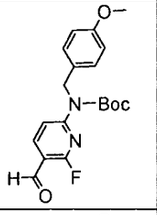
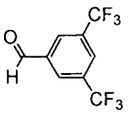
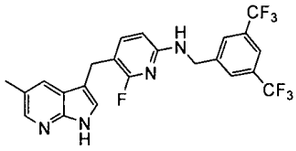
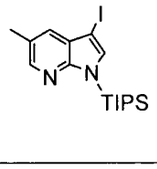
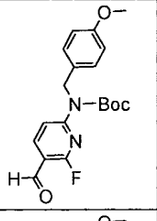
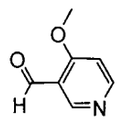
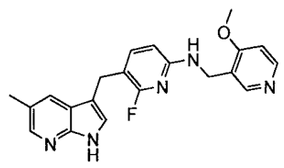
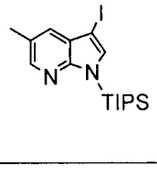
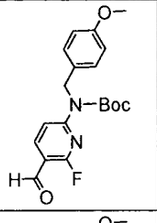
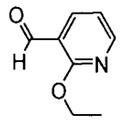
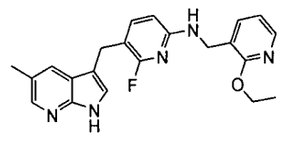
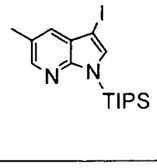
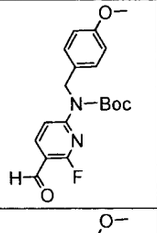
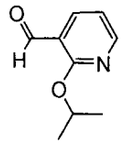
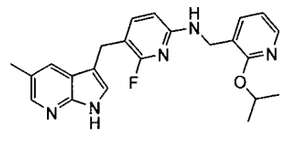
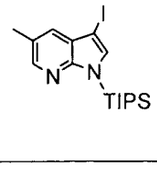
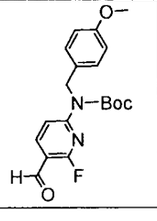
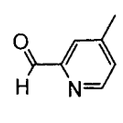
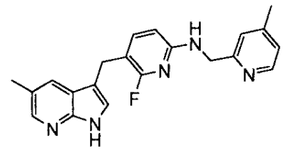
Número de comp.	pirrolo[2,3-b]piridina	Boc Aldehído	Aldehído de Etapa 3	Compuesto	MS (ESI) $[M+H^+]^+$
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P-1570					

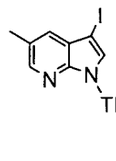
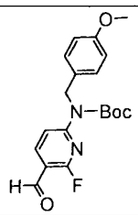
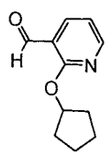
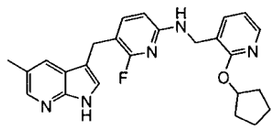
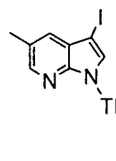
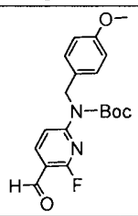
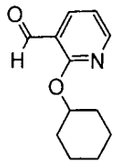
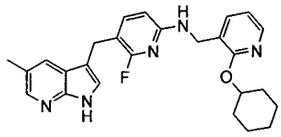
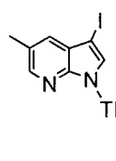
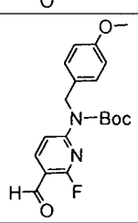
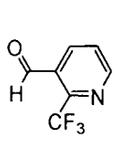
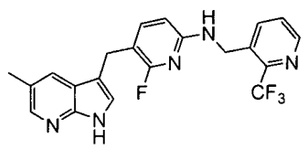
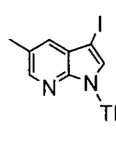
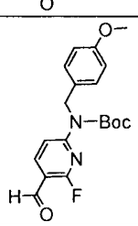
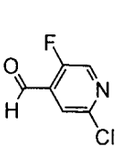
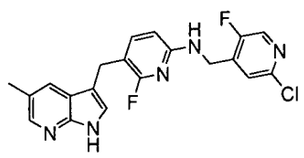
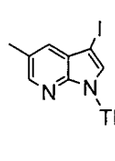
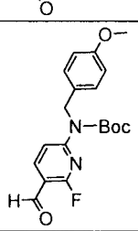
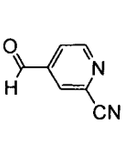
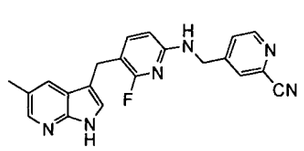
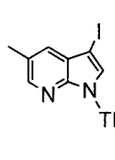
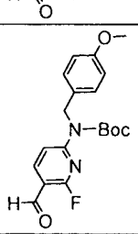
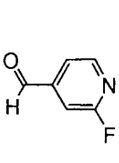
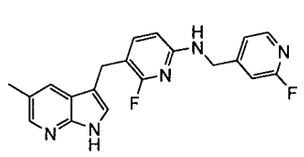
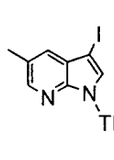
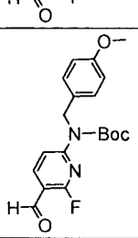
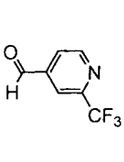
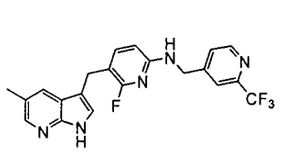
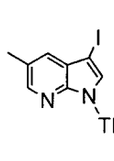
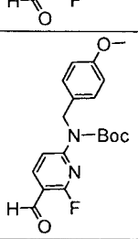
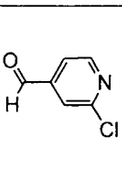
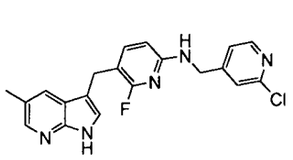
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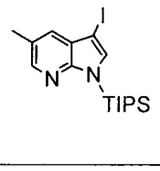
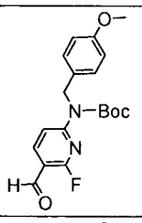
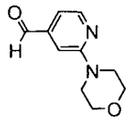
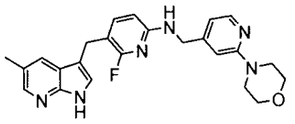
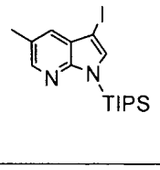
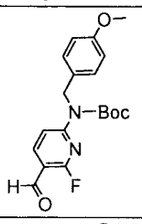
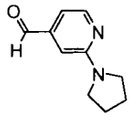
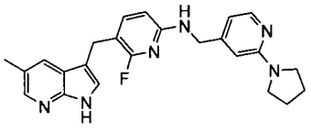
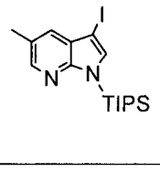
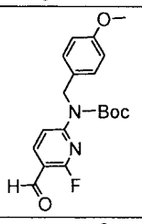
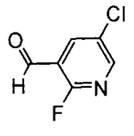
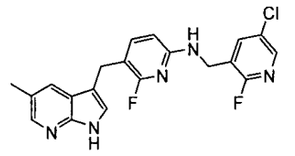
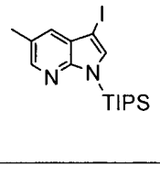
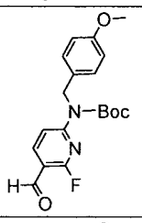
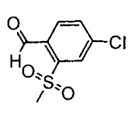
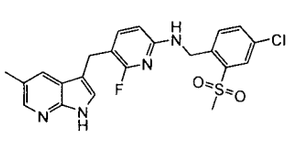
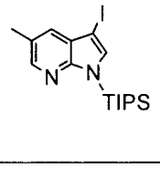
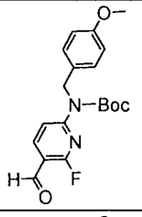
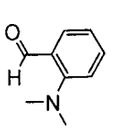
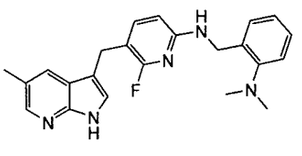
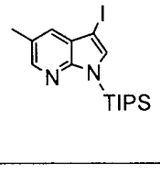
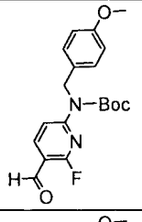
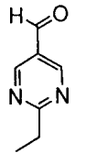
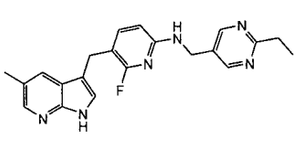
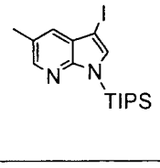
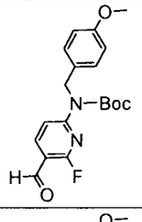
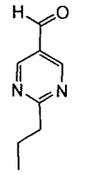
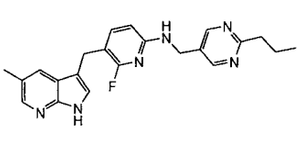
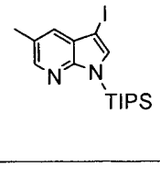
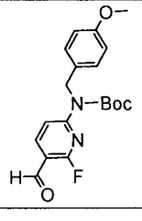
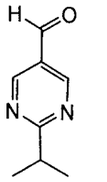
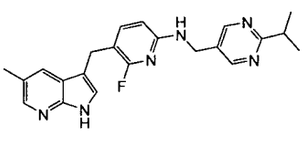
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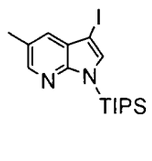
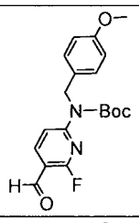
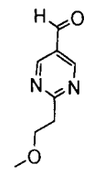
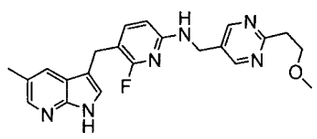
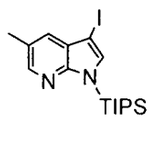
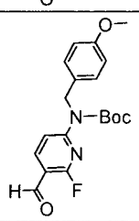
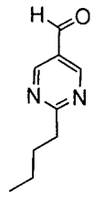
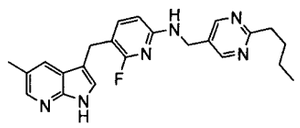
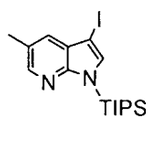
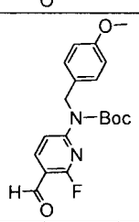
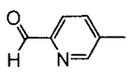
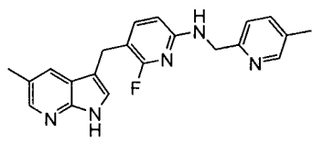
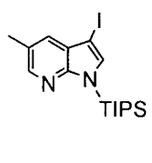
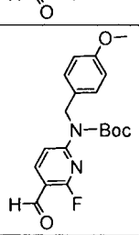
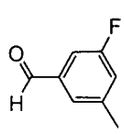
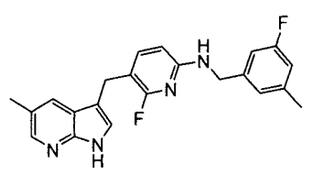
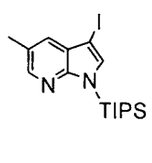
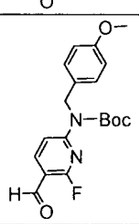
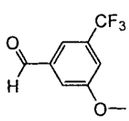
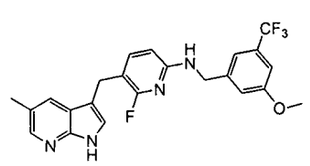
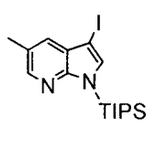
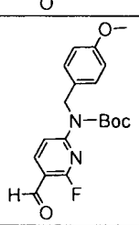
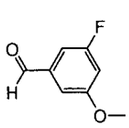
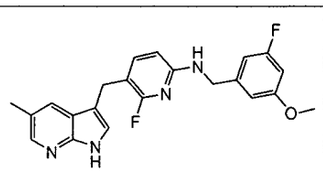
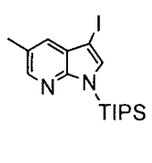
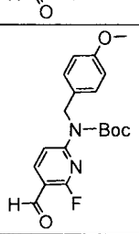
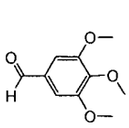
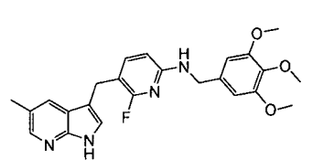
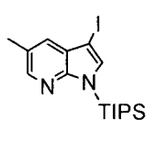
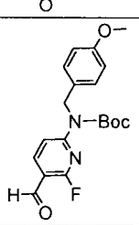
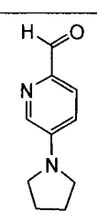
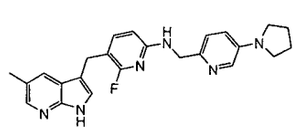
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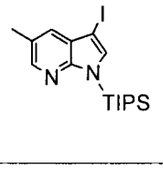
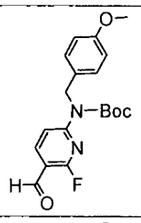
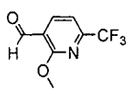
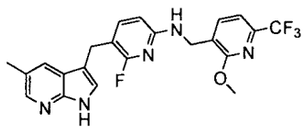
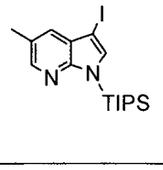
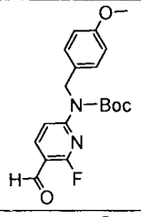
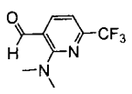
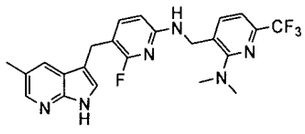
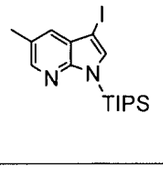
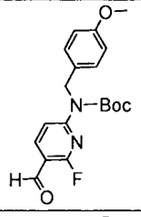
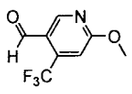
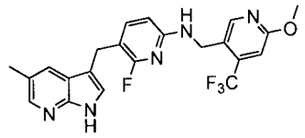
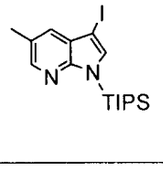
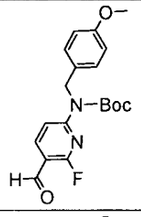
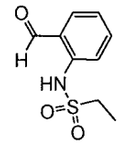
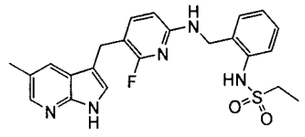
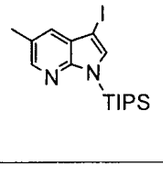
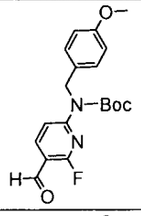
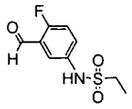
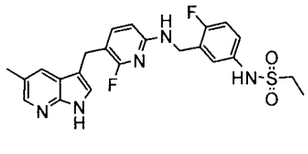
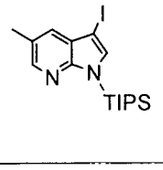
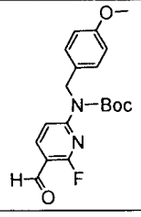
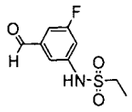
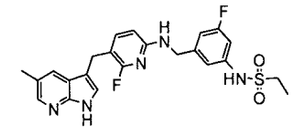
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P-2098					443.1
P-2099					382.3
P-2100					
P-2101					
P-2102					
P-2103					366.3
P-2104					

P-2105					378.3
P-2106					
P-2107					
P-2108					
P-2109					378.3
P-2110					
P-2111					
P-2112					

P-2113					
P-2114					
P-2115					416.3
P-2116					
P-2117					
P-2118					366.3
P-2119					416.3
P-2120					382.3

P-2121					
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P-2123					
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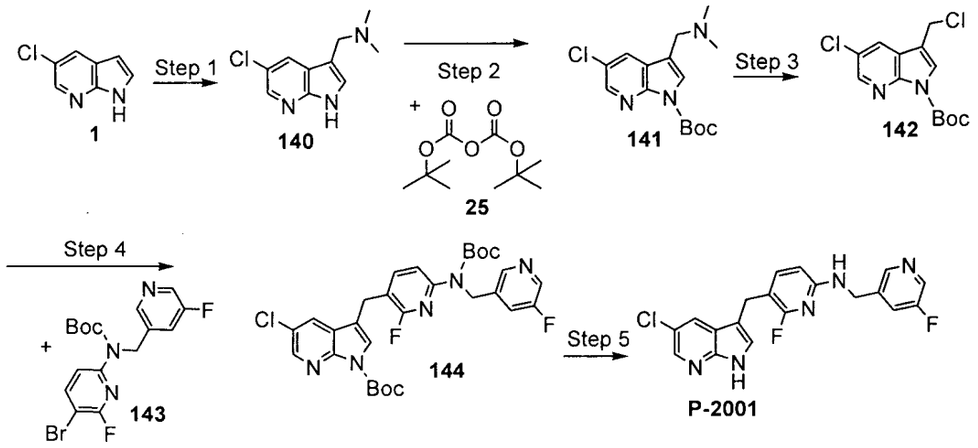
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P-2130					
P-2131					362.3
P-2132					
P-2133					
P-2134					395.1
P-2150					
P-2151					

P-2166 (etapa 3a)					446.2
P-2167 (etapa 3a)					459.1
P-2186 (etapa 3a)					446.4
P-2198 (etapa 3a)					454.0
P-2199 (etapa 3a)					472.0
P-2202 (etapa 3a)					472.1

Ejemplo 17: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina P-2001.

[0375] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **P-2001** se preparó en cinco etapas a partir de 5-cloro-1H-pirrolo[2,3-b]piridina **1** como se muestra en el Esquema 17.

Esquema 17



*Etapa 1 – Preparación de (5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-dimetil-amina (**140**):*

[0376] A 5-cloro-1H-pirrolo[2,3-b]piridina (**1**, 8.00 g, 0.0524 mol) en 250 ml de alcohol isopropílico, clorhidrato de dimetilamina (4.79 g, 0.0587 mol) y formaldehído (1.77 g, 0.0589 mol) se agregaron. La reacción se agitó a temperatura ambiente durante la noche, seguido por reflujo durante 4 horas. La reacción se concentró, se vertió en agua, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró para dar el compuesto sin purificar (**140**, 10.0 g, 91%), que se usó directamente en la siguiente etapa.

*Etapa 2: Preparación de ter-butiléster del ácido 5-cloro-3-dimetilaminometil-pirrolo[2,3-b]piridin-1-carboxílico (**141**)*

[0377] A (5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-dimetil-amina (**140**, 5.00 g, 23.8 mmol,) en 60.0 ml de N,N-dimetilformamida, hidruro de sodio (1.05 g, 60% en aceite mineral, 26.2 mmol) se agregó. Después de 10 minutos, di-ter-butildicarbonato (**25**, 6.24 g, 28.6 mmol) se agregó y la reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 5% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**141**, 5.20 g).

*Etapa 3: Preparación de ter-butiléster del ácido 5-cloro-3-clorometil-pirrolo[2,3-b]piridin-1-carboxílico (**142**)*

[0378] A ter-butiléster del ácido 5-cloro-3-dimetilaminometil-pirrolo[2,3-b]piridin-1-carboxílico (**141**, 4.20 g, 13.6 mmol) en 100 ml de tolueno, cloroformiato de etilo (1.48 ml, 15.5 mmol) se agregó bajo nitrógeno. La reacción se agitó a temperatura ambiente durante 2 horas, luego se concentró bajo vacío y se combinó con agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 25% de acetato de etilo en hexano para proporcionar el compuesto deseado (**142**, 1.60 g).

*Etapa 4 – Preparación de ter-butiléster del ácido 3-{6-[ter-butoxicarbonil-(5-fluoro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-5-cloro-pirrolo[2,3-b]piridin-1-carboxílico (**144**):*

[0379] A ter-butiléster del ácido (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-piridin-3-ilmetil)-carbámico (**143**, 0.600 g, 1.50 mmol) en 10.0 ml de tetrahidrofurano a -25 °C bajo nitrógeno, cloruro de isopropilmagnesio (0.730 ml, 2.0 M en tetrahidrofurano, 1.46 mmol) se agregó y la reacción se dejó llegar a 5 °C durante 1 hora. La reacción luego se enfrió a -35 °C, y CuCN·2LiCl (2.0 ml, 0.75 M en tetrahidrofurano, 1.5 mmol) se agregó. Después de 5 minutos, ter-butiléster del ácido 5-cloro-3-clorometil-pirrolo[2,3-b]piridin-1-carboxílico (**142**, 0.300 g, 0.996 mmol) en 4.0 ml de tetrahidrofurano se agregó y la reacción se dejó llegar a temperatura ambiente durante 1 hora. La reacción se vertió en solución diluida de amoniaco y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y el solvente se removió bajo vacío para proporcionar el compuesto deseado (**144**, 130 mg). MS (ESI) $[M+H^+]^+ = 586.2$.

*Etapa 5 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2001**):*

[0380] A ter-butiléster del ácido 3-{6-[ter-butoxicarbonil-(5-fluoro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-5-cloro-pirrolo[2,3-b]piridin-1-carboxílico (**144**, 0.280 g, 0.478 mmol) en 10.0 ml de diclorometano, ácido trifluoroacético (1.00 ml, 13.0 mmol) se agregó y la reacción se agitó a temperatura ambiente durante la noche. Este se combinó con una reacción separada desarrollada de manera similar y se concentró bajo vacío. El material resultante se combinó con carbonato de potasio acuoso y acetato de etilo y se mezcló. La capa acuosa se separó y la capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y el solvente se removió bajo vacío para proporcionar el compuesto deseado (**P-2001**, 99 mg). MS (ESI) $[M+H^+]^+ = 386.0$.

Preparación de 3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204)**

[0381] A 5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina (125 mg, 0.27 mmol) se agregó 2 ml de N,N-dimetilacetamida. La suspensión mezclada se desgasificó por burbujeo con argón. A esta suspensión se agregó Zinc (5 mg, 0.08 mmol), 11,1'-Bis(difenilfosfino)ferroceno (6 mg, 0.01 mmol), Cianuro de Zinc (0.01 ml, 0.19 mmol), y Tris(dibencilidenoacetona)dipaladio (0) (7 mg, 0.01 mmol) a temperatura ambiente bajo argón. La mezcla se calentó a 120 °C durante 2 horas y se enfrió a temperatura ambiente. La mezcla de reacción se extrajo con acetato de etilo y agua (+cloruro de sodio saturado). La capa orgánica se

lavó con agua y salmuera, se secó por $MgSO_4$. Los compuestos volátiles se removieron bajo vacío. El residuo se suspendió en acetonitrilo y se sometió a ultrasonido durante 45 minutos. El precipitado se recolectó por filtración y se lavó con acetonitrilo. Un sólido marrón se obtuvo (98 mg, 88.8% de rendimiento). LC-MS mostró un pico principal con 98.6 % de pureza. La estructura del producto se confirma por H^1-NMR(DMSO-d6). MS (ESI) $[M+H]^+ = 406.9$.

[0382] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 17, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan reemplazando opcionalmente 5-cloro-1H-pirrolo[2,3-b]piridina **1** con una 1H-pirrolo[2,3-b]piridina 5-sustituida adecuada en la etapa 1 y reemplazando opcionalmente ter-butiléster del ácido (5-bromo-6-fluoro-piridin-2-il)-(5-fluoro-piridin-3-ilmetil)-carbámico **143** con un compuesto de bromo (u otro halógeno adecuado) N-protegido adecuado en la etapa 4. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1654**),

3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1655**),

3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1656**),

3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1657**),

3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1658**),

3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1659**),

3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-1660**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2027**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2028**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

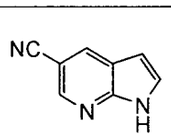
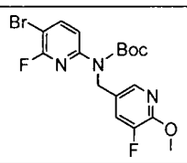
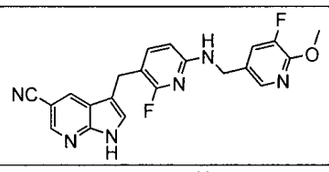
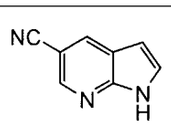
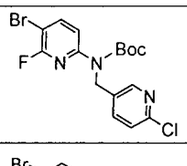
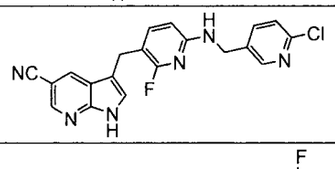
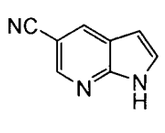
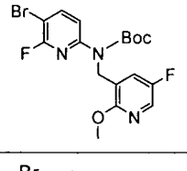
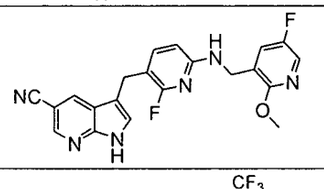
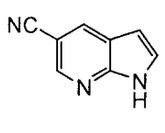
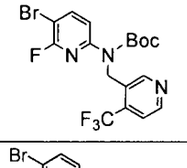
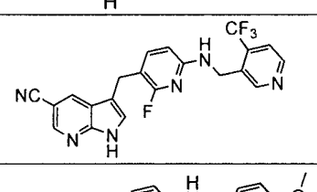
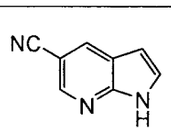
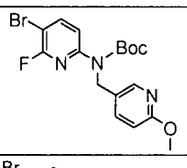
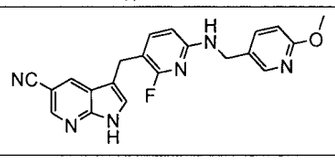
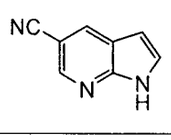
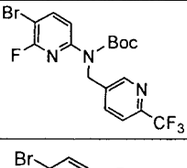
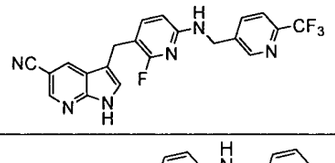
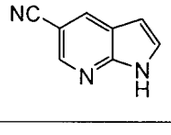
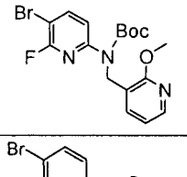
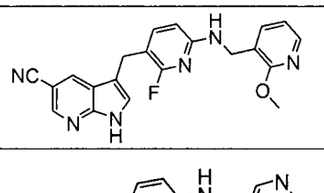
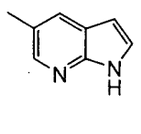
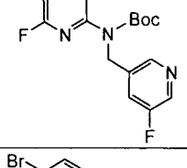
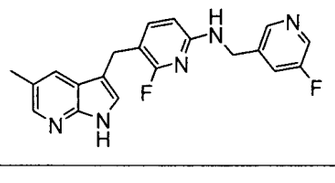
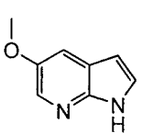
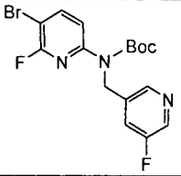
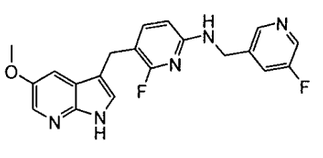
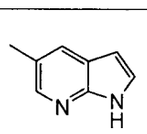
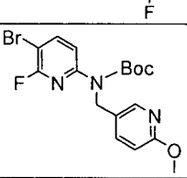
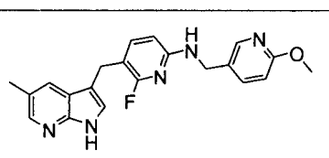
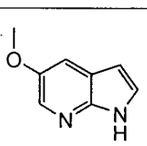
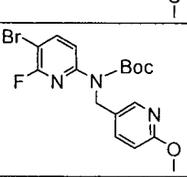
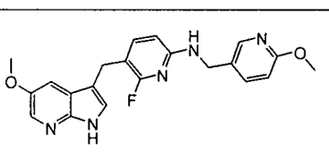
(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2041**),

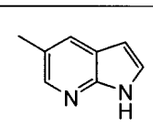
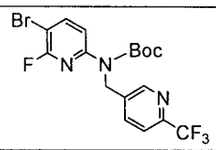
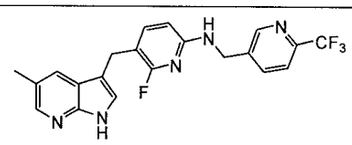
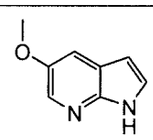
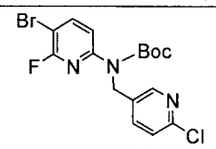
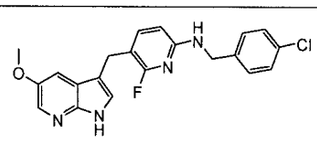
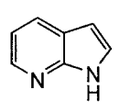
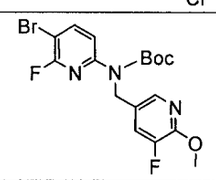
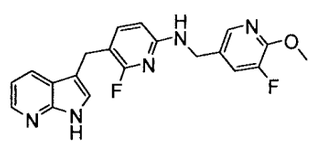
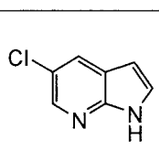
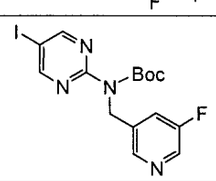
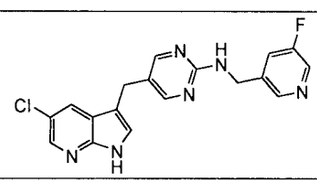
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2176**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),** y

6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**.

La siguiente tabla indica el compuesto 1H-pirrolo[2,3-b]piridina (columna 2) usado en la etapa 1 y el compuesto sustituido con halógeno (columna 3) usado en la etapa 4 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de comp.	1H-pirrolo[2,3-b]piridina	Compuesto de halógeno	Estructura del compuesto	MS (ESI) $[M+H^+]^+$

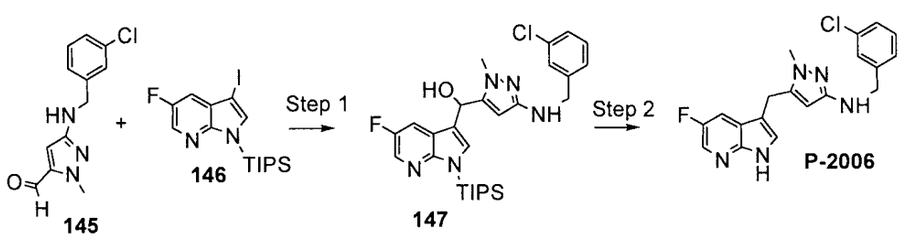
P-1654				
P-1655				
P-1656				407.2
P-1657				
P-1658				
P-1659				
P-1660				
P-2027				366.0
P-2028				381.9
P-2029				378.0
P-2030				394.2

P-2031				381.9
P-2032				396.9
P-2041				
P-2176				369.1

Ejemplo 18: Síntesis de (3-cloro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina P-2006.

[0383] (3-Cloro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina **P-2006** se preparó en dos etapas a partir de 5-(3-cloro-bencilamino)-2-metil-2H-pirazol-3-carbaldehído **145** y 5-fluoro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **146** como se muestra en el Esquema 18.

Esquema 18



*Etapa 1 – Preparación de [5-(3-cloro-bencilamino)-2-metil-2H-pirazol-3-il]-(5-fluoro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**147**):*

[0384] 5-Fluoro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**146**, 0.33 g, 0.79 mmol) y 1.5 ml de tetrahidrofurano se combinaron en un matraz de fondo redondo y se enfriaron a -20 °C. Cloruro de isopropilmagnesio (400 µL, 2.0 M en tetrahidrofurano, 0.8 mmol) se agregó por goteo y la reacción se agitó y se llevó a -5 °C. La reacción se enfrió a -20 °C y 5-(3-cloro-bencilamino)-2-metil-2H-pirazol-3-carbaldehído (**145**, 0.090 g, 0.36 mmol) en tetrahidrofurano se agregó y la reacción se agitó y se llevó a 0 °C. La reacción se concentró bajo vacío, se diluyó con acetato de etilo y se lavó con bicarbonato de sodio acuoso saturado, luego salmuera. La capa orgánica se separó y se secó

sobre sulfato de sodio, se filtró y el filtrado se purificó por cromatografía de columna instantánea en gel de sílice eluyendo con un gradiente de 5-80% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+$ = 542.7, 543.95.

*Etapa 2 – Preparación de (3-cloro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina (**P-2006**):*

[0385] A [5-(3-cloro-bencilamino)-2-metil-2H-pirazol-3-il]-(5-fluoro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**147**, 0.070 g, 0.13 mmol) en 4 ml de diclorometano, trietilsilano (0.210 ml, 1.31 mmol) y ácido trifluoroacético (0.100 ml, 1.30 mmol) se agregaron y la reacción se agitó durante la noche a temperatura ambiente. La reacción se concentró bajo vacío, luego acetato de etilo se agregó, luego se lavó con 1M carbonato de potasio acuoso, luego salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se purificó por cromatografía de columna instantánea en gel de sílice eluyendo con un gradiente de 2-20% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío y el sólido resultante se lavó con acetato de etilo en hexano para proporcionar el compuesto deseado.

[0386] Los siguientes compuestos se preparan siguiendo el protocolo del Esquema 18, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los siguientes compuestos se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

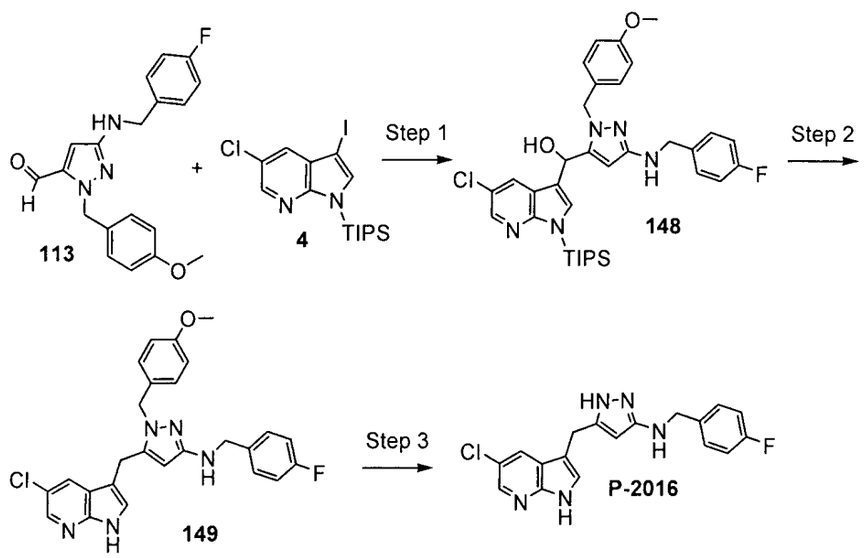
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),** y

6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)**.

Ejemplo 19: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina P-2016.

[0387] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **P-2016** se preparó en tres etapas a partir de 5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carbaldehído **113** y 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **4** como se muestra en el Esquema 19.

Esquema 19



*Etapa 1 – Preparación de (5-cloro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-[5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-il]-metanol (**148**):*

[0388] En un matraz de fondo redondo, 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**4**, 1.7 g, 3.9 mmol) se combinó con 1.3 ml de tetrahidrofurano y se enfrió a -20 °C. Cloruro de isopropilmagnesio (2.0 ml, 2 M en tetrahidrofurano, 4.0 mmol) se agregó por goteo y la reacción se agitó a -5 °C. La reacción se enfrió a -20 °C y 5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-carbaldehído (**113**, 0.622 g, 1.83 mmol) en 2 ml de tetrahidrofurano se agregó y la reacción se agitó a 0 °C. La reacción se concentró bajo vacío, se diluyó con acetato de etilo y se lavó con bicarbonato de sodio y salmuera. La capa orgánica se secó con sulfato de sodio y se purificó por cromatografía de columna en gel de sílice, eluyendo con 5-80% de acetato de etilo en hexanos. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado. MS (ESI) $[M+H^+]^+ = 648.38$ y 649.74.

*Etapa 2 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-(4-metoxi-bencil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**149**):*

[0389] En un vial de cuarzo, (5-cloro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-[5-(4-fluoro-bencilamino)-2-(4-metoxi-bencil)-2H-pirazol-3-il]-metanol (**148**, 0.328 g, 0.506 mmol) se combinó con 20 ml de diclorometano, trietilsilano (0.4 ml, 2.0 mmol) se agregó, seguido por ácido trifluoroacético (0.2 ml, 2.0 mmol). La reacción se agitó durante la noche a temperatura ambiente, luego se concentró bajo vacío y acetato de etilo se agregó. Este se lavó con 1 M carbonato de potasio acuoso y salmuera, se secó con sulfato de sodio, y se purificó por cromatografía de columna en gel de sílice, eluyendo con 2-20% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío, y el sólido se lavó además con acetato de etilo y hexano para proporcionar el compuesto deseado. ^{1}H NMR fue consistente con la estructura del compuesto.

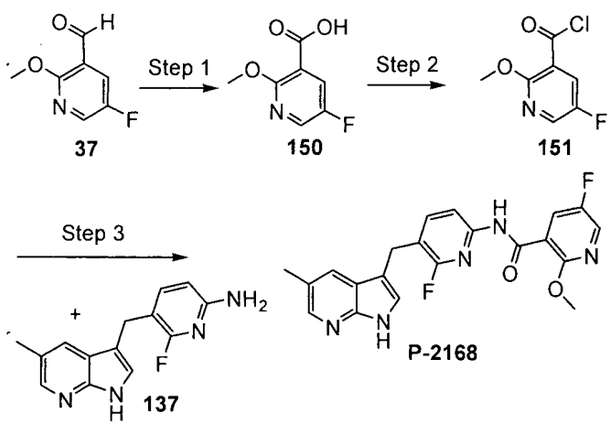
*Etapa 3 – Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**P-2016**):*

[0390] En un matraz de fondo redondo, [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-(4-metoxi-bencil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**149**, 0.060 g, 0.13 mmol) se disolvió en 5 ml de ácido trifluoroacético (60 mmol) y la reacción se calentó a 70 °C durante la noche. La reacción se enfrió a temperatura ambiente, luego se concentró bajo vacío y acetato de etilo se agregó. Este se lavó con 1 M carbonato de potasio acuoso y salmuera, se secó con sulfato de sodio y se purificó por cromatografía de columna en gel de sílice, eluyendo con 2-20% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío, y el sólido se lavó además con acetato de etilo y hexano para proporcionar el compuesto deseado. ^{1}H NMR fue consistente con la estructura del compuesto. MS (ESI) $[M+H^+]^+ = 356.85$.

Ejemplo 20: Síntesis de 5-fluoro-N-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-2-metoxi-nicotinamida P-2168.

[0391] 5-Fluoro-N-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-2-metoxi-nicotinamida **P-2168** se preparó en tres etapas a partir de 5-fluoro-2-metoxi-piridin-3-carbaldehído **37** como se muestra en el Esquema 20.

Esquema 20



*Etapa 2 – Preparación de ácido 5-fluoro-2-metoxi-nicotínico (**150**):*

[0392] En un matraz de fondo redondo, 5-fluoro-2-metoxi-piridin-3-carbaldehído (**37**, 0.500 g, 3.22 mmol) se combinó con clorito de sodio (0.6734 g, 5.957 mmol), 30 ml de 1,4-dioxano, 10 ml de agua, y ácido sulfámico (2.39 g, 24.6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos, luego se vertió en 100 ml de agua y se extrajo con 100 ml de acetato de etilo. La capa orgánica se lavó con agua, salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado (**150**, 512 mg), usado en la siguiente etapa sin purificación adicional.

*Etapa 2 – Preparación de cloruro de 5-fluoro-2-metoxi-nicotinoilo (**151**):*

[0393] En un matraz de fondo redondo, ácido 5-fluoro-2-metoxi-nicotínico (**150**, 250 mg, 1.46 mmol) se combinó con cloruro de tionilo (3.00 ml, 41.1 mmol) y la suspensión se agitó a temperatura ambiente durante 3 horas. La reacción se concentró a sequedad bajo vacío para proporcionar el compuesto deseado, usado en la siguiente etapa sin purificación adicional.

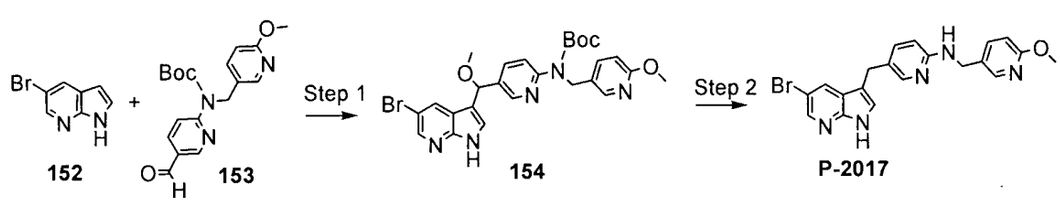
*Etapa 3 – Preparación de 5-fluoro-N-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-2-metoxi-nicotinamida (**P-2168**):*

[0394] En un matraz de reacción, 6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**137**, 100 mg, 0.3902 mmol) se combinó con cloruro de 5-fluoro-2-metoxi-nicotinoilo (**151**, 81.37 mg, 0.4292 mmol), 3.00 ml de tetrahidrofurano, y piridina (0.06312 ml, 0.7804 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en ácido clorhídrico acuoso 1N y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 1-5% de metanol en diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**P-2168**, 100 mg). MS (ESI) $[M+H^+]^+ = 409.9$.

Ejemplo 21: Síntesis de [5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina P-2017.

[0395] [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **P-2017** se preparó en dos etapas a partir de 5-bromo-1H-pirrolo[2,3-b]piridina **152** y ter-butiléster del ácido (5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **153** como se muestra en el Esquema 21.

Esquema 21



*Etapa 1 – Preparación ter-butiléster del ácido {5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-metoxi-metil]-piridin-2-il}-(6-metoxi-piridin-3-ilmetil)-carbámico (**154**):*

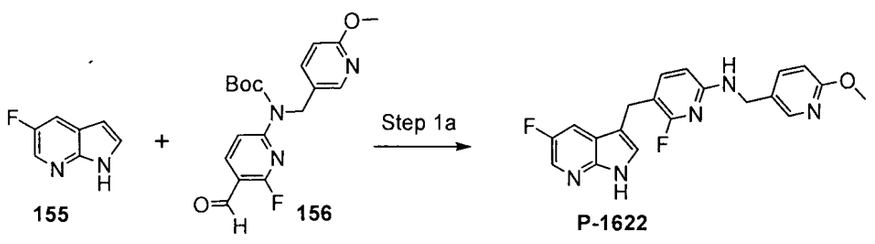
[0396] A 5-bromo-1H-pirrolo[2,3-b]piridina (**152**, 0.622 g, 3.16 mmol) en 50.0 ml de metanol bajo nitrógeno, ter-butiléster del ácido (5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico (**153**, 1.05 g, 3.06 mmol) e hidróxido de potasio (1.50 g, 26.7 mmol) se agregaron y la reacción se agitó a temperatura ambiente durante la noche. La reacción se vertió en agua, se extrajo con acetato de etilo,

la capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con un gradiente de 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**154**, 0.35 g). ter-butiléster del ácido {5-[(5-Bromo-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il}-(6-metoxi-piridin-3-ilmetil)-carbámico también se formó en este procedimiento y puede aislarse y hacerse reaccionar de manera similar a la siguiente etapa para formar el producto deseado.

*Etapa 2 – Preparación de [5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2017**):*

[0397] A ter-butiléster del ácido {5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-metoxi-metil]-piridin-2-il}-(6-metoxi-piridin-3-ilmetil)-carbámico (**154**, 0.35 g, 0.63 mmol) en 20.0 ml de acetonitrilo, trietilsilano (1.0 ml, 6.3 mmol) y ácido trifluoroacético (0.50 ml, 6.5 mmol) se agregaron y la reacción se agitó a 80 °C durante 4 horas. La reacción se concentró bajo vacío y se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**P-2017**, 165.1 mg). MS (ESI) $[M+H^+]^+ = 423.8$, 425.8.

[0398] [6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **P-1622** se prepara de manera similar al Esquema 21, haciendo reaccionar en una sola etapa 1a como sigue.



*Etapa 1a – Preparación de [6-fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1622**):*

[0399] En un matraz de fondo redondo, 5-fluoro-1H-pirrolo[2,3-b]piridina (**155**, 0.115 g, 0.845 mmol) se combinó con ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico (**156**, 0.397 g, 1.10 mmol), 2.60 ml de acetonitrilo, ácido trifluoroacético (0.325 ml, 4.22 mmol) y trietilsilano (0.810 ml, 5.07 mmol) y la reacción se calentó a reflujo durante 3 horas. La reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se

purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo en hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**P-1622**, 28 mg). MS (ESI) $[M+H^+]^+ = 382.1$.

[0400] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 21 (o única etapa 1a), donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan opcionalmente usando una 1H-pirrolo[2,3-b]piridina adecuada en lugar de 5-bromo-1H-pirrolo[2,3-b]piridina **152** y opcionalmente usando un aldehído adecuado en lugar de ter-butiléster del ácido (5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **153** en la etapa 1. Además, cualquiera o los dos, el intermediario metoxi o hidroxi formado en la etapa 1 se hacen reaccionar en la segunda etapa. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1506**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1507**),

(6-Cloro-piridin-3-ilmetil)-[6-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1508**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1509**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1510**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1511**),

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1512**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1528**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1529**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1530**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1531**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1583**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1584**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1585**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1586**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1587**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1588**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1589**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1590**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1591**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-cloro-piridin-3-ilmetil)-amina (**P-1592**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1593**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1594**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1595**),

[6-Cloro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1596**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1623**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1624**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1625**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1626**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1627**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1628**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1629**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1638**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1639**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1640**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1641**),

(4-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1642**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1643**),

(6-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1644**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1645**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1661**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1662**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1663**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1664**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1665**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1666**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1667**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1668**),

3-{6-[(5-Fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1719**),

3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1720**),

3-{6-[(5-Fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1721**),

3-{6-[(4-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1722**),

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1723**),

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1724**),

3-{6-[(2-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1725**),

3-{6-[(5-Fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-4-carbonitrilo (**P-1726**),

[5-(4-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2018**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

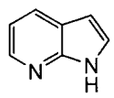
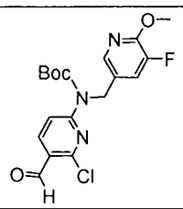
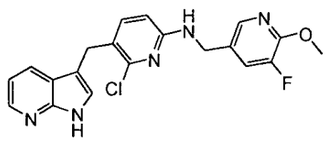
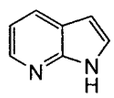
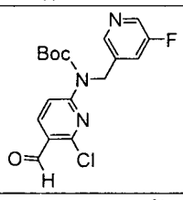
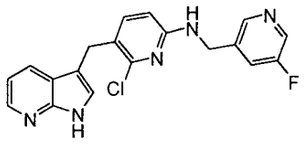
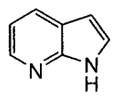
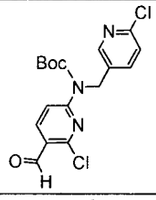
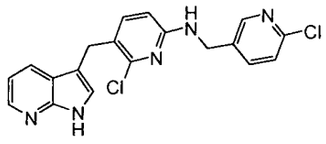
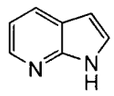
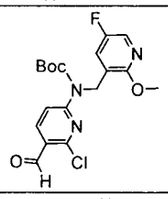
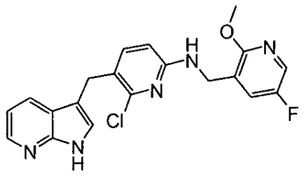
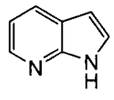
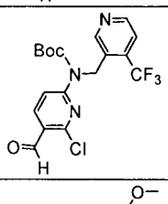
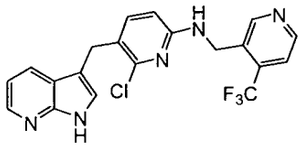
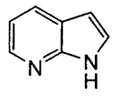
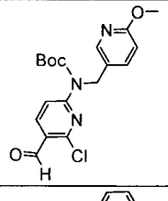
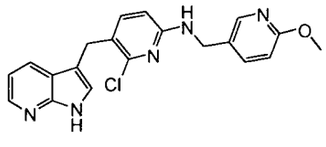
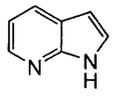
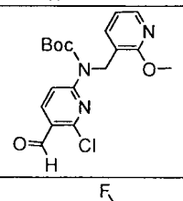
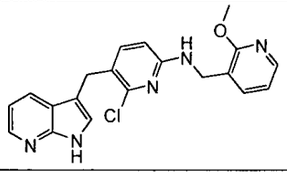
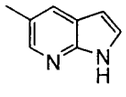
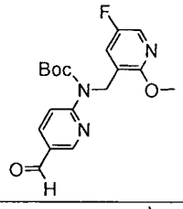
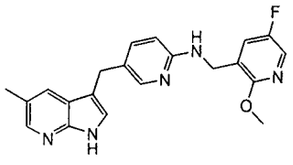
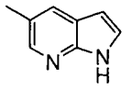
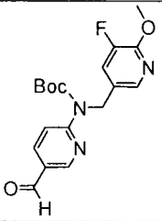
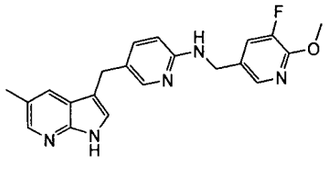
[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2023**),

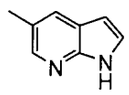
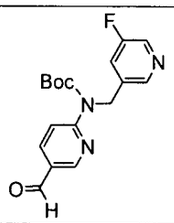
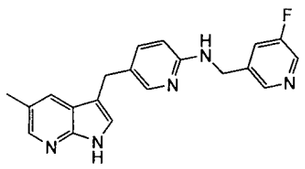
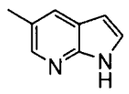
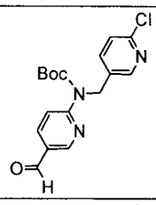
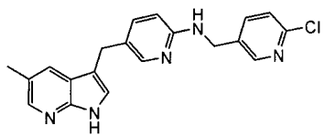
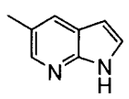
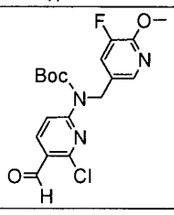
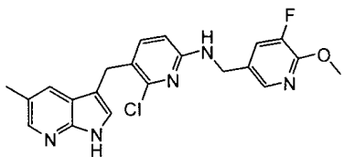
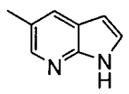
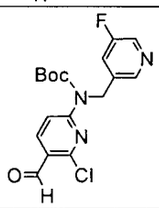
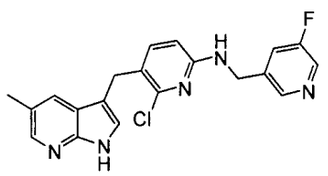
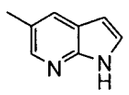
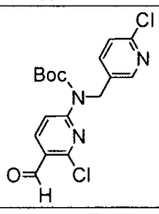
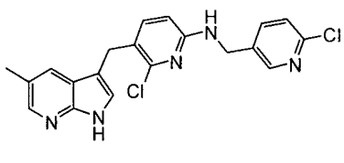
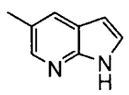
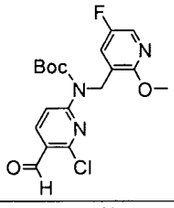
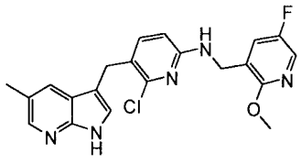
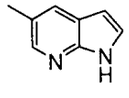
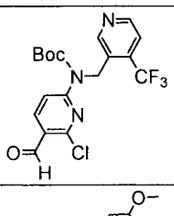
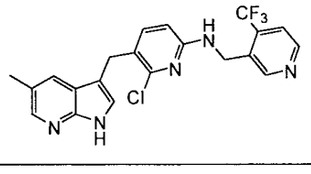
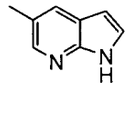
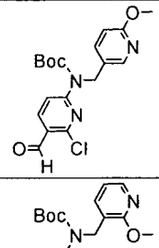
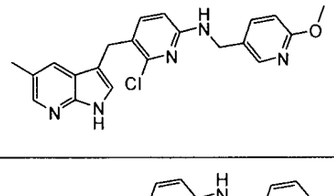
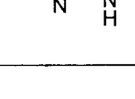
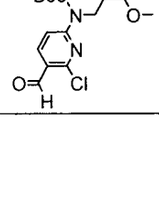
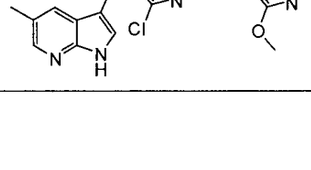
(2-Fluoro-bencil)-[5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2033**), y

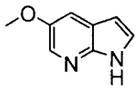
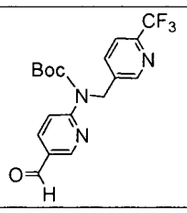
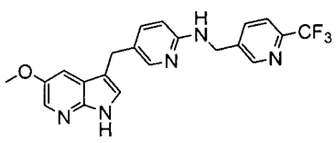
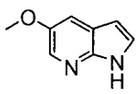
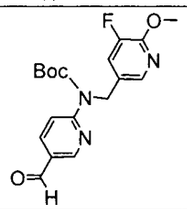
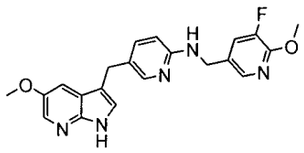
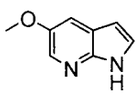
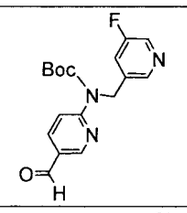
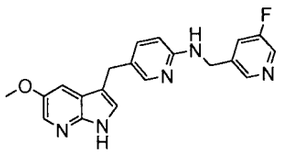
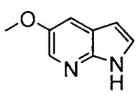
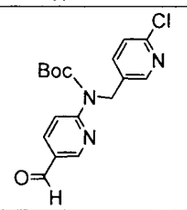
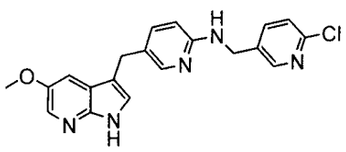
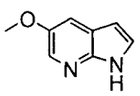
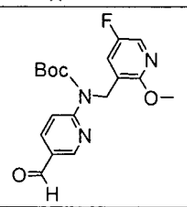
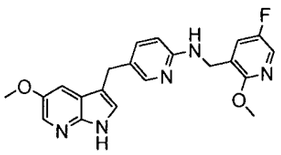
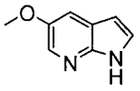
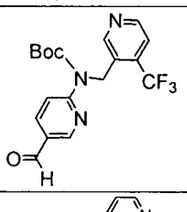
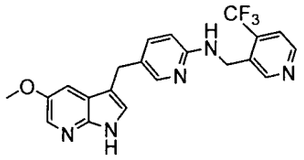
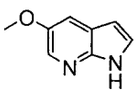
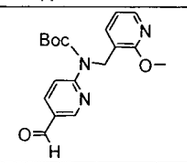
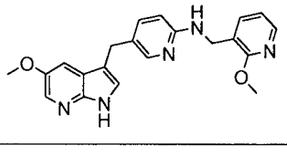
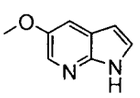
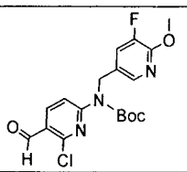
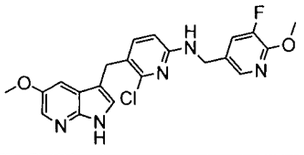
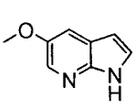
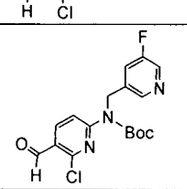
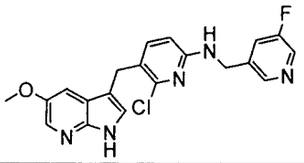
[5-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2170**).

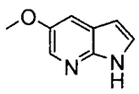
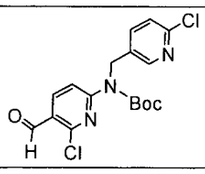
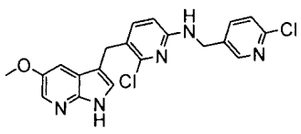
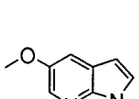
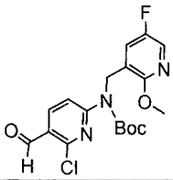
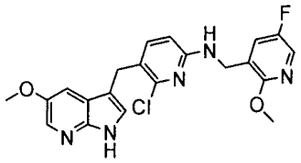
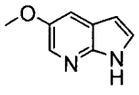
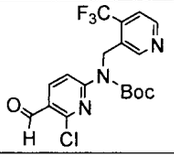
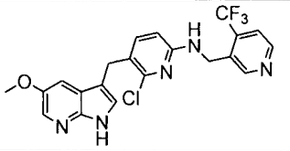
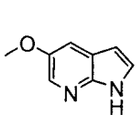
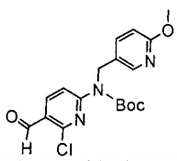
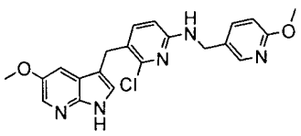
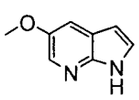
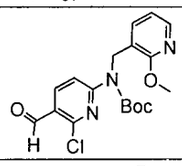
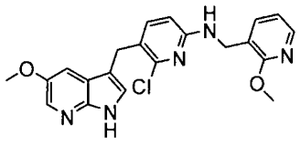
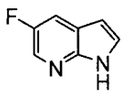
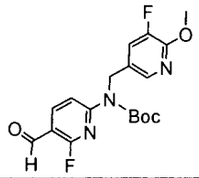
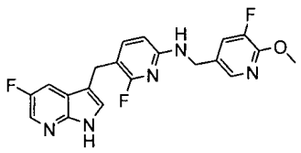
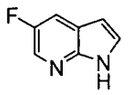
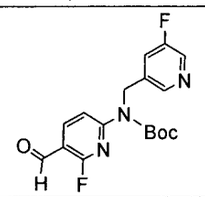
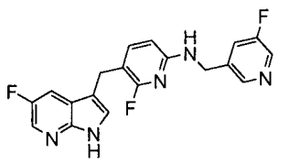
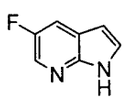
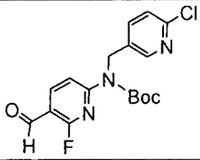
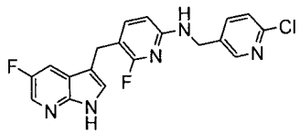
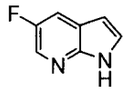
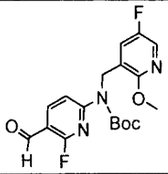
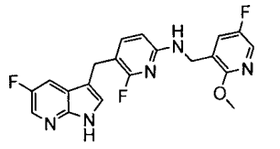
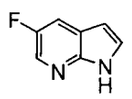
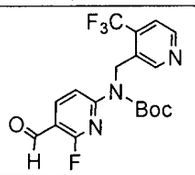
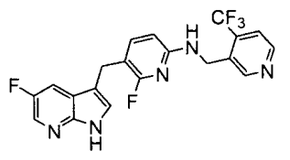
La siguiente tabla indica el compuesto 1H-pirrolo[2,3-b]piridina (columna 2) y el compuesto aldehído (columna 3) usado en la etapa 1 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

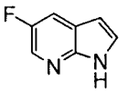
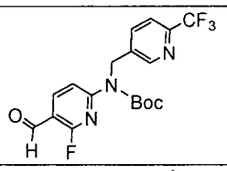
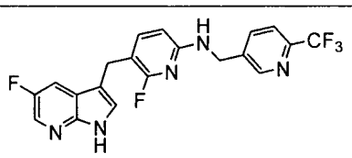
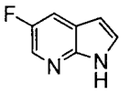
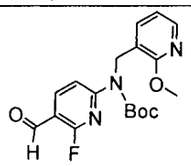
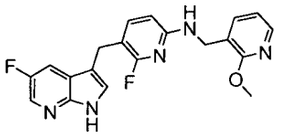
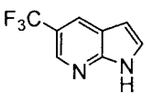
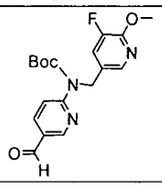
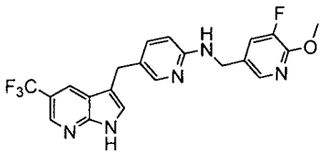
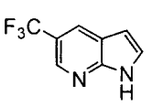
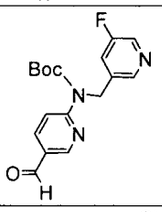
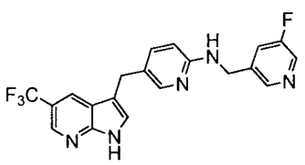
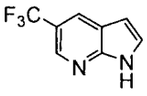
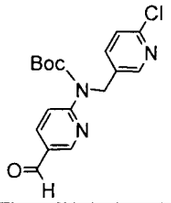
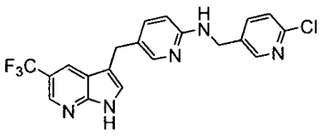
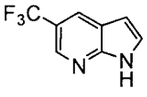
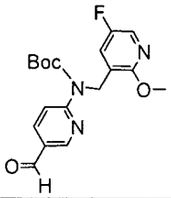
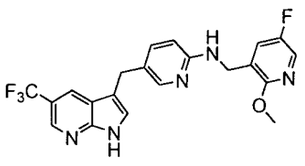
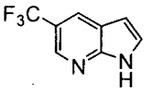
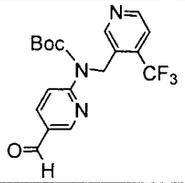
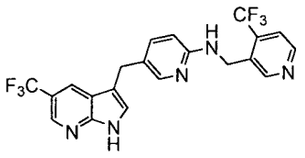
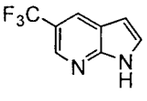
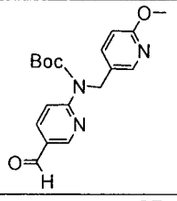
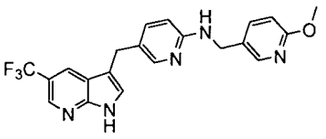
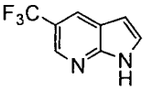
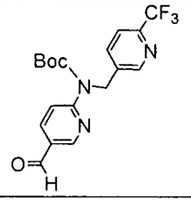
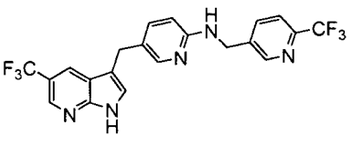
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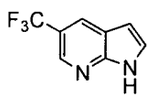
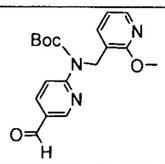
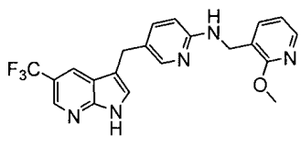
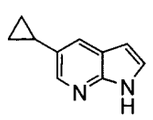
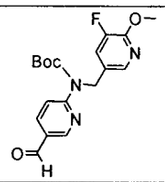
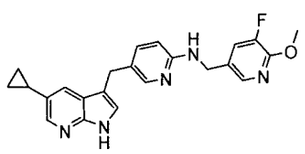
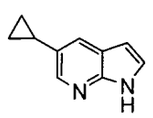
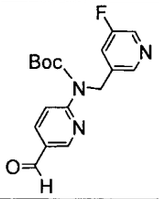
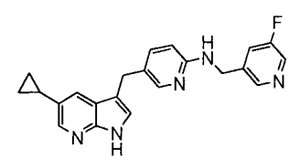
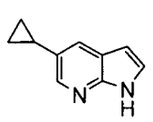
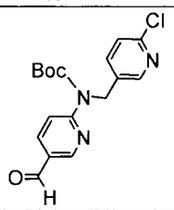
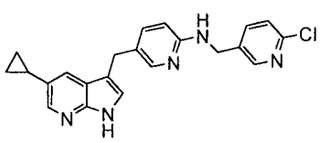
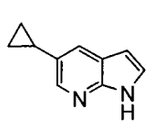
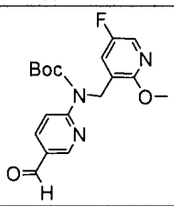
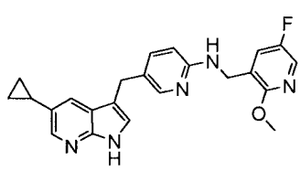
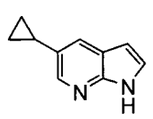
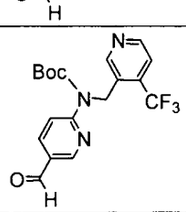
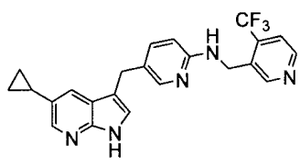
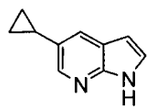
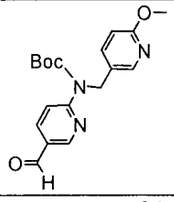
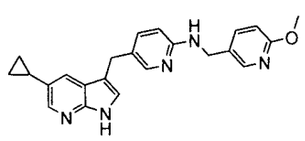
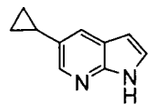
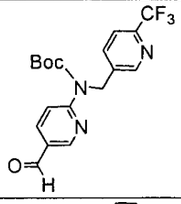
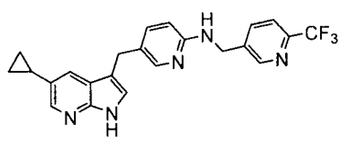
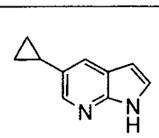
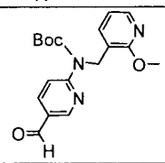
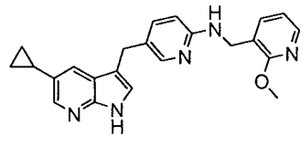
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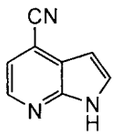
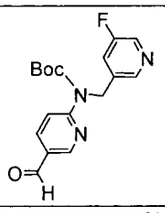
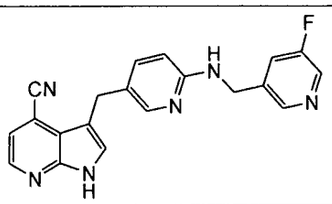
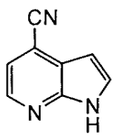
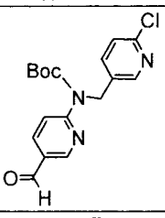
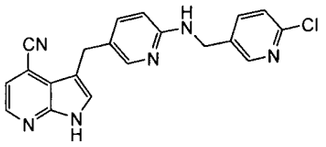
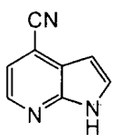
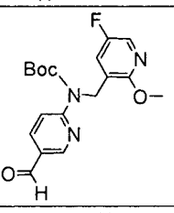
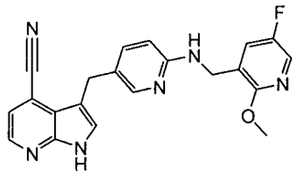
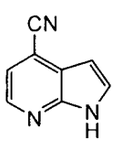
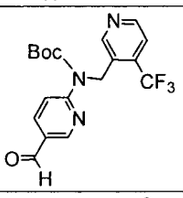
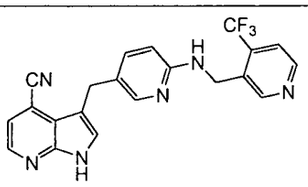
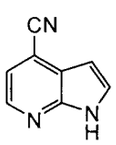
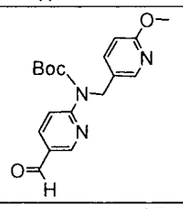
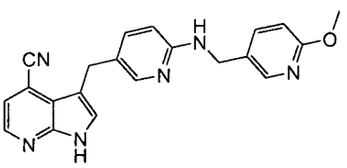
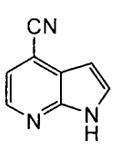
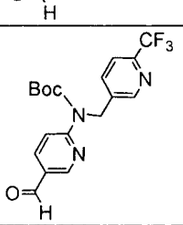
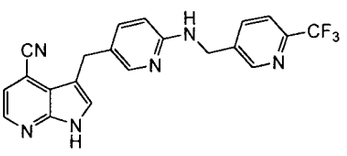
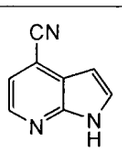
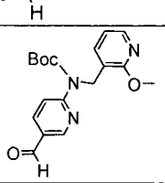
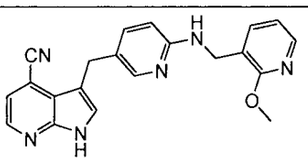
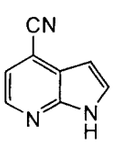
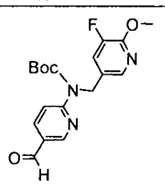
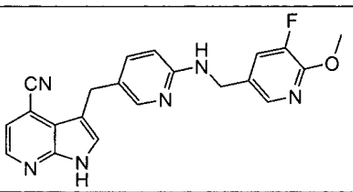
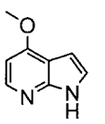
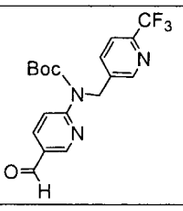
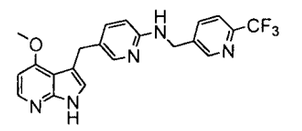
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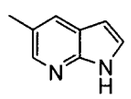
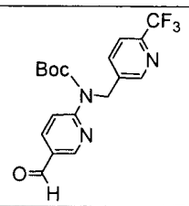
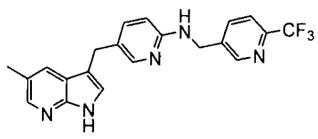
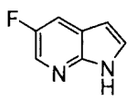
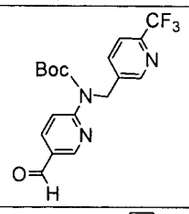
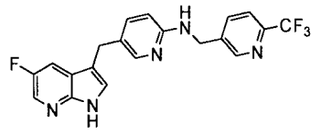
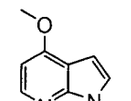
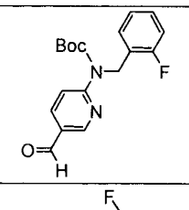
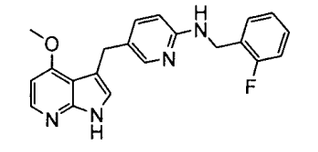
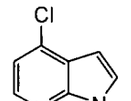
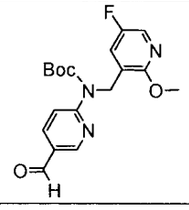
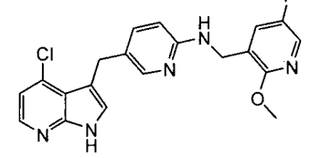
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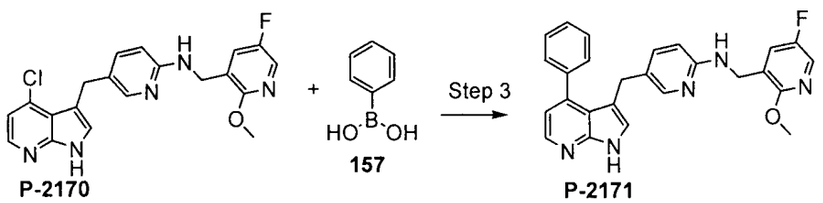
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P-1725				
P-1726				
P-2018				

P-2019				398.4
P-2023				
P-2033				363.5
P-2170				

[0401] [5-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina **P-2170** se hace reaccionar además para proporcionar (5-fluoro-2-metoxi-piridin-3-ilmetil)-[5-(4-fenil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-2171** siguiendo el protocolo de la siguiente etapa 3.



P-2170 **157** **P-2171**

*Etapa 3 – Preparación de 5-fluoro-2-metoxi-piridin-3-ilmetil)-[5-(4-fenil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2171**):*

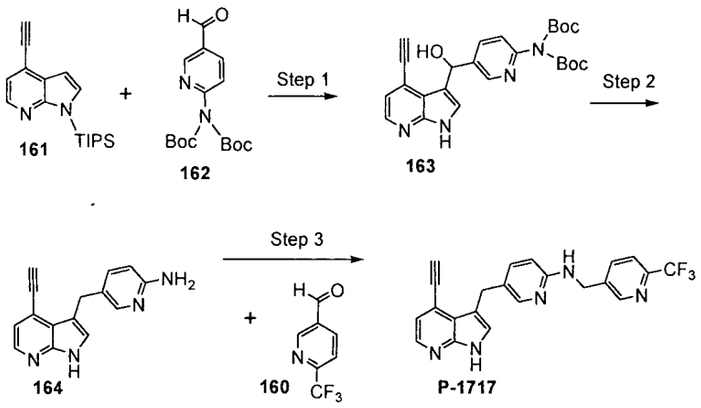
[0402] [5-(4-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (P-2170, 1 equivalente), ácido fenil borónico (**157**, 1.5 equivalentes) y tetrakis(trifenilfosfina)paladio(0) (catalizador) se combinan con 0.33 ml de carbonato de potasio acuoso (1.00 M, 3 equivalentes) y 0.34 ml de acetonitrilo. La mezcla resultante se calentó en un horno de microondas a 120 °C durante 10 minutos, seguido por 130 °C durante 55 minutos. La mezcla se diluyó con acetato de etilo y agua y la capa acuosa se separó y se extrajo con acetato de etilo. Las capas orgánicas se combinaron y se lavaron con salmuera, se secaron sobre sulfato de

sodio, se filtraron y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

Ejemplo 22: Síntesis de [5-(4-etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorómetil-piridin-3-ilmetil)-amina P-1717.

[0403] [5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-1717** se preparó en tres etapas a partir de 4-etinil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **161** y ter-butiléster del ácido (5-formil-piridin-2-il)-di-carbámico **162** como se muestra en el Esquema 22.

Esquema 22



*Etapa 1 – Preparación de ter-butiléster del ácido {5-[(4-etinil-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il}-di-carbámico (**163**):*

[0404] En un matraz de fondo redondo, 4-etinil-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**161**, 0.321 g, 1.08 mmol) se combinó con ter-butiléster del ácido (5-formil-piridin-2-il)-di-carbámico (**162**, 0.416 g, 1.29 mmol), 2.1 ml de metanol, e hidróxido de potasio (0.302 g, 5.38 mmol) y se agitó a temperatura ambiente durante 24 horas. La reacción se neutralizó con ácido clorhídrico acuoso 0.1 N, luego se extrajo 3x con acetato de etilo. La capa orgánica combinada se lavó con salmuera, luego se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**163**, 229 mg). MS (ESI) $[M-H^+]^-$ = 337.2.

*Etapa 2 – Preparación de 5-(4-etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**164**):*

[0405] En un matraz de fondo redondo, ter-butiléster del ácido {5-[(4-etinil-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il}-di-carbámico (**163**, 0.225 g, 0.484 mmol) se combinó con ácido trifluoroacético (0.70 ml, 9.1 mmol), trietilsilano (1.8 ml, 11.0 mmol) y 5.2 ml de acetonitrilo y

la reacción se calentó a reflujo durante 6 horas. La reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, luego se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**164**, 57 mg). MS (ESI) $[M+H^+]^+$ = 248.9.

*Etapa 3 – Preparación de [5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1717**):*

[0406] En un matraz de fondo redondo, 5-(4-etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**164**, 0.055 g, 0.22 mmol) se combinó con 6-trifluorometil-piridin-3-carbaldehído (**160**, 50.4 mg, 0.288 mmol), 0.682 ml de acetonitrilo, ácido trifluoroacético (0.0853 ml, 1.11 mmol), y trietilsilano (0.212 ml, 1.33 mmol) y la reacción se calentó a reflujo durante 3 horas. La reacción se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, luego se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con metanol y diclorometano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**P-1717**, 9.3 mg). MS (ESI) $[M+H^+]^+$ = 408.5.

[0407] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 22, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan reemplazando opcionalmente 6-trifluorometil-piridin-3-carbaldehído **160** con un aldehído adecuado en la etapa 3. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1711**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1712**),

(6-Cloro-piridin-3-ilmetil)-[5-(4-etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1713**),

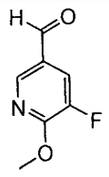
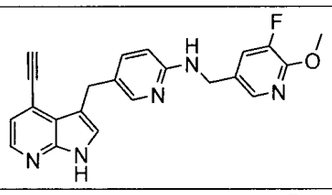
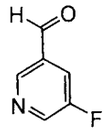
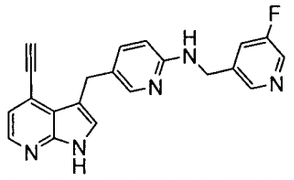
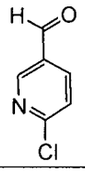
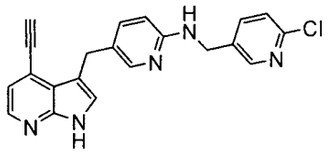
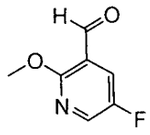
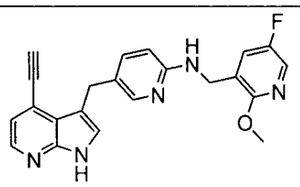
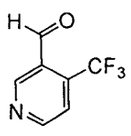
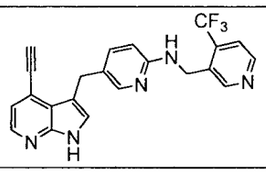
[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1714**),

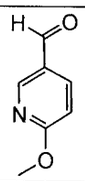
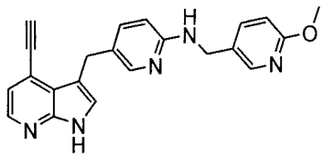
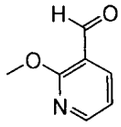
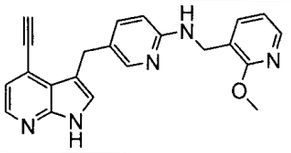
[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1715**),

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1716**), y

[5-(4-Etinil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1718**).

La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 3 para proporcionar el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

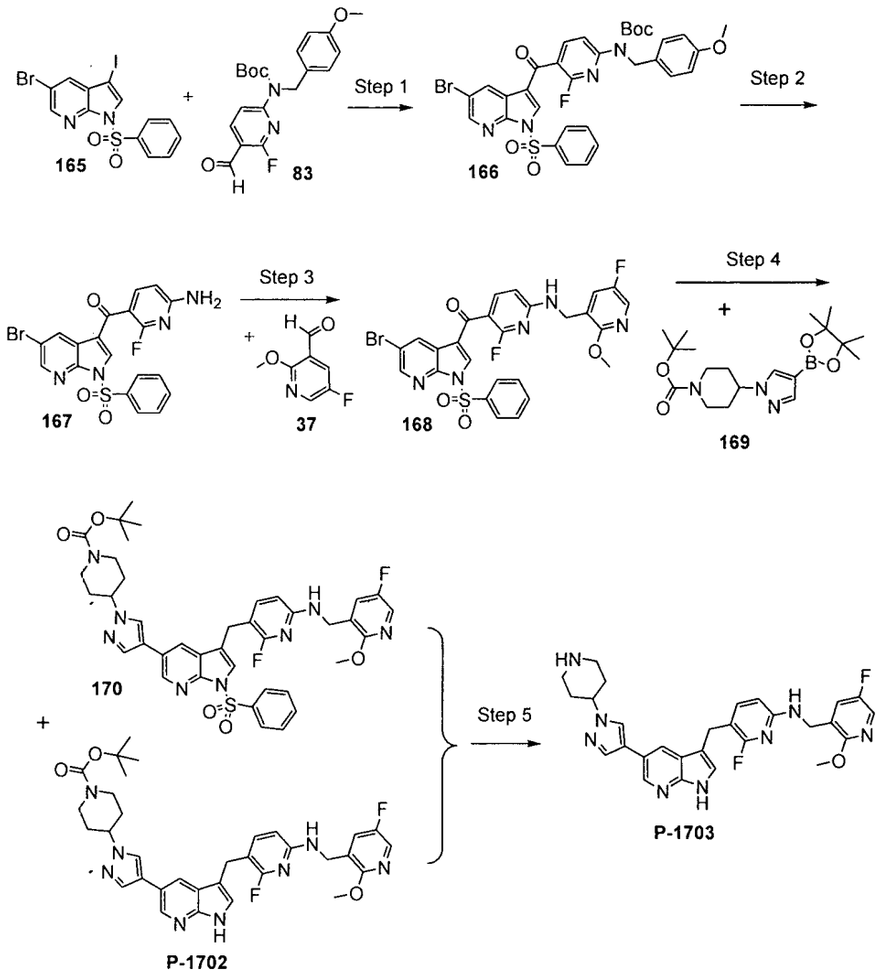
Número de compuesto	Aldehído	Compuesto	MS (ESI) $[M+H^+]^+$
P-1711			
P-1712			
P-1713			
P-1714			
P-1715			

P-1716			
P-1718			

Ejemplo 23: Síntesis de (5-fluoro-2-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina P-1703.

[0408] (5-Fluoro-2-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina **P-1703** se preparó en cinco etapas a partir de 1-bencenosulfonil-5-bromo-3-yodo-1H-pirrolo[2,3-b]piridina **165** y ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico **83** como se muestra en el Esquema 23.

Esquema 23



*Etapa 1 – Preparación de ter-butiléster del ácido {5-[(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-6-fluoro-piridin-2-il}-(4-metoxi-bencil)-carbámico (**166**):*

[0409] . A una solución de 1-bencenosulfonil-5-bromo-3-yodo-1H-pirrolo[2,3-b]piridina (**165**, 1.00 g, 2.16 mmol) en 7 ml de tetrahidrofurano a -50 °C bajo nitrógeno, cloruro de isopropilmagnesio (1.18 ml, 2.35 mmol) se agregó lentamente. La reacción se calentó a 5 °C durante 70 minutos, luego se enfrió a -45 °C y ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico (**83**, 0.678 g, 1.88 mmol) en 3.0 ml de tetrahidrofurano se agregó. La reacción se dejó calentar a temperatura ambiente durante 2-3 horas. La reacción se mezcló con ácido cítrico acuoso 1 N y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**166**, 1.155 g). MS (ESI) $[M+H^+]^+$ = 696.4 y 698.3.

*Etapa 2 – Preparación de 5-(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-ilamina (**167**):*

[0410] En un matraz de fondo redondo, ter-butiléster del ácido {5-[(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-6-fluoro-piridin-2-il}-(4-metoxi-bencil)-carbámico (**166**, 1.15 g, 1.65 mmol) se combinó con 50 ml de 1,2-dicloroetano, ácido trifluoroacético (0.635 ml, 8.24 mmol), y trietilsilano (1.32 ml, 8.24 mmol). La reacción se calentó a reflujo durante 20 horas, luego se concentró bajo vacío. El residuo se disolvió en 10 ml de ácido trifluoroacético y se agitó a temperatura ambiente durante 18 horas, luego se concentró bajo vacío y se combinó con bicarbonato de sodio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato de sodio, agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado (**167**, 403 mg). MS (ESI) $[M-H^+]^-$ = 460.8 y 462.8.

*Etapa 3 – Preparación de [5-(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**168**):*

[0411] A 5-(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-ilamina (**167**, 0.342 g, 0.741 mmol) en 10 ml de acetonitrilo, 5-fluoro-2-metoxi-piridin-3-carbaldehído (**37**, 0.118 g, 0.763 mmol), trietilsilano (0.529 ml, 3.71 mmol) y ácido trifluoroacético (0.286 ml, 3.71 mmol) se agregaron. La reacción se calentó a 80 °C durante 4 horas, luego se concentró bajo vacío y se combinó con carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar el compuesto deseado como un sólido blanquecino (**168**, 367 mg). MS (ESI) $[M-H^+]^-$ = 599.6 y 601.6.

*Etapa 4 – Preparación de ter-butiléster del ácido 4-[4-(1-bencenosulfonil-3-{2-fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-pirazol-1-il]-piperidin-1-carboxílico (**170**) y ter-butiléster del ácido 4-[4-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-pirazol-1-il]-piperidin-1-carboxílico (**P-1702**):*

[0412] En un vial para horno de microondas, [5-(1-bencenosulfonil-5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**168**, 218 mg, 0.363 mmol) y ter-butiléster del ácido 4-[4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-pirazol-1-il]-piperidin-1-carboxílico (**169**, 205 mg, 0.545 mmol) se combinaron y 2.22 ml de acetonitrilo y carbonato de potasio (1.11 ml, 1.0 M en agua, 1.11 mmol) se agregaron. Luego [1,1'-

bis(difenilfosfino)ferroceno]dicloropaladio(II) (27 mg, 0.037 mmol) se agregó a la mezcla de reacción y se calentó a 160 °C en un horno de microondas durante 5 minutos. Se agregó agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo y hexano. Las fracciones apropiadas se combinaron y concentraron bajo vacío para proporcionar los compuestos deseados (**170**, 137 mg) y (**P-1702**, 66 mg). **170** MS (ESI) $[M+H^+]^+ = 770.7$. **P-1702** MS (ESI) $[M+H^+]^+ = 631.1$.

*Etapa 5 – Preparación de (5-fluoro-2-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1703**):*

[0413] En un vial, ter-butiléster del ácido 4-[4-(1-bencenosulfonil-3-{2-fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-pirazol-1-il]-piperidin-1-carboxílico (**170**, 0.137 g, 0.178 mmol) se disolvió en una solución de hidróxido de potasio (0.392 g, 6.99 mmol) en 7.0 ml de metanol y la reacción se calentó a 50 °C durante 3 horas. Ácido cítrico acuoso 1 M se agregó, luego la reacción se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera, luego se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío. ter-butiléster del ácido 4-[4-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-pirazol-1-il]-piperidin-1-carboxílico (**P-1702**, 56 mg, 0.0888 mmol) se combinó con este y 10 ml de diclorometano y ácido trifluoroacético (0.50 ml, 6.5 mmol) se agregaron, luego se agitó a temperatura ambiente durante 2 horas. Bicarbonato de sodio saturado acuoso se agregó a pH~8, luego se concentró bajo vacío y se agregaron acetato de etilo y agua. La capa orgánica se aisló y se lavó con bicarbonato de sodio saturado acuoso, luego se secó con sulfato de magnesio, se filtró y el filtrado se concentró bajo vacío para proporcionar el compuesto deseado como un sólido amarillo (**P-1703**, 74 mg). MS (ESI) $[M+H^+]^+ = 631.1$.

[0414] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 23, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan reemplazando opcionalmente 5-fluoro-2-metoxi-piridin-3-carbaldehído **37**, con un aldehído adecuado en la etapa 3. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^1H y ^{13}C así como espectrometría de masas.

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1704**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(5-fluoro-piridin-3-ilmetil)-amina (**P-1705**),

(6-Cloro-piridin-3-ilmetil)-{6-fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-amina (**P-1706**),

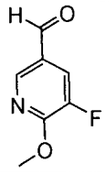
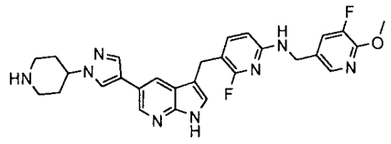
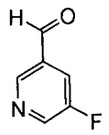
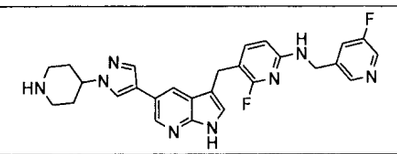
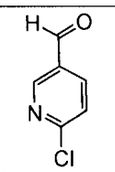
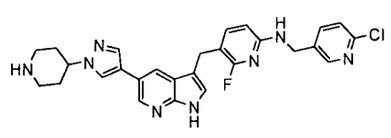
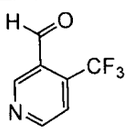
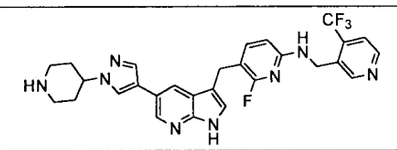
{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1707**),

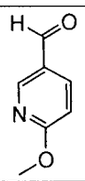
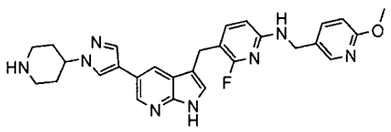
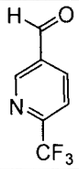
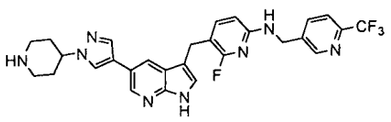
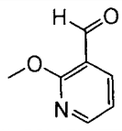
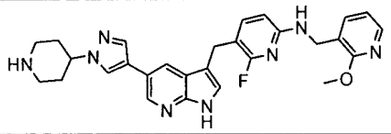
{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(6-metoxi-piridin-3-ilmetil)-amina (**P-1708**),

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1709**), y

{6-Fluoro-5-[5-(1-piperidin-4-il-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-piridin-2-il}-(2-metoxi-piridin-3-ilmetil)-amina (**P-1710**).

La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 3 para proporcionar el compuesto deseado (columna 3). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 4.

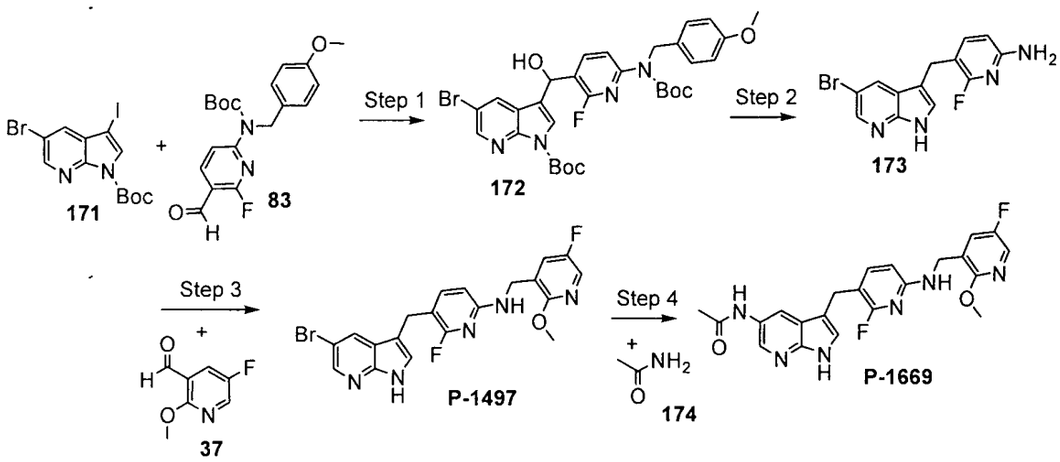
Número de compuesto	Aldehído	Compuesto	MS (ESI) $[M+H^+]^+$
P-1704			
P-1705			
P-1706			
P-1707			

P-1708			
P-1709			
P-1710			

Ejemplo 24: Síntesis de N-(3-{2-fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida P-1669.

[0415] N-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida **P-1669** se prepara en cuatro etapas a partir de ter-butiléster del ácido 5-bromo-3-yodo-pirrolo[2,3-b]piridin-1-carboxílico **171** y ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico **83** como se muestra en el Esquema 24.

Esquema 24



Etapa 1 – Preparación de ter-butiléster del ácido 5-bromo-3-({6-[ter-butoxicarbonil-(4-metoxi-bencil)-amino]-2-fluoro-piridin-3-il}-hidroxi-metil)-pirrolo[2,3-b]piridin-1-carboxílico (172):

[0416] A ter-butiléster del ácido 5-bromo-3-yodo-pirrolo[2,3-b]piridin-1-carboxílico (**171**, 1 equivalente) en 500 ml de tetrahidrofurano bajo nitrógeno a -20 °C, cloruro de iso-propilmagnesio (1.2 equivalente) se agrega. La reacción se dejó calentar a 0 °C durante 30 minutos, luego se enfrió a

-40 °C, seguido la adición de ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(4-metoxi-bencil)-carbámico (**83**, 0.8 equivalente). La reacción se dejó calentar a 0 °C durante una hora, luego se extinguió con salmuera y se extrajo con acetato de etilo. La capa orgánica se concentró bajo vacío para proporcionar el compuesto deseado, usado en la siguiente etapa sin purificación adicional.

Etapa 2 – Preparación de 5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-ilamina (173):

[0417] A ter-butiléster del ácido 5-bromo-3-({6-[ter-butoxicarbonil-(4-metoxi-bencil)-amino]-2-fluoro-piridin-3-il}-hidroxi-metil)-pirrolo[2,3-b]piridin-1-carboxílico (**172**, 1 equivalente) en 451 ml de acetonitrilo, trietilsilano (10 equivalentes) y ácido trifluoroacético (10 equivalentes) se agregan. La reacción se agitó a 80 °C durante varias horas, luego se concentró bajo vacío. El material resultante se recogió en 250 ml de diclorometano y 250 ml de ácido trifluoroacético se agregaron, luego se agitó a reflujo durante varias horas. La reacción se concentró bajo vacío y el material resultante se recogió en acetato de etilo y se extrajo con la adición de carbonato de potasio acuoso saturado. La capa orgánica se concentró bajo vacío y el material resultante se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-5% de metanol en diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

*Etapa 3 – Preparación de [5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1497**):*

[0418] A 5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-ilamina (**173**, 1 equivalente) y 5-fluoro-2-metoxi-piridin-3-carbaldehído (**37**, 1 equivalente), trietilsilano (4 equivalentes) y ácido trifluoroacético (4 equivalentes) se agregan. La reacción se agitó a 80 °C durante varias horas, luego se concentró bajo vacío. El material resultante se recogió en acetato de etilo y se extrajo con adición de carbonato de potasio acuoso. La capa orgánica se concentró bajo vacío, luego se trituró con diclorometano para proporcionar el compuesto deseado.

*Etapa 4 – Preparación de N-(3-{2-fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1669**):*

[0419] [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1497**, 1 equivalente) se disolvió en 25 ml de dioxano en un vial que puede sellarse. Carbonato de cesio (2.1 equivalentes), yoduro de cobre(I) (1.5 equivalentes), acetamida (**174**, 22 equivalentes) y N,N'-dimetiletilenodiamina (17 equivalentes) se agregan. El vial se selló y se calentó a 100 °C durante la noche. La reacción se agregó a acetato de etilo y salmuera y se extrajo. La capa orgánica se concentró bajo vacío y el material resultante se disolvió en diclorometano y se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-10% de metanol en diclorometano. Las fracciones apropiadas se concentraron, y el material se disolvió en tetrahidrofurano para purificación adicional en una columna C18 de fase inversa, eluyendo con 0-

100% de metanol (con 10% tetrahidrofurano)/agua. Las fracciones apropiadas se combinan y concentran bajo vacío. El material resultante se trituró con metil ter-butil éter y se filtró, lavando con metil ter-butil éter, luego heptano. El sólido se secó bajo vacío para proporcionar el compuesto deseado.

[0420] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 24, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan reemplazando opcionalmente 5-fluoro-2-metoxi-piridin-3-carbaldehído **37**, con un aldehído adecuado en la etapa 3 y reemplazando opcionalmente acetamida **174** con metanosulfonamida en la etapa 4. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

N-(3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1670**),

N-(3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1671**),

N-(3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1672**),

N-(3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1673**),

N-(3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1674**),

N-(3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1675**),

N-(3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1676**),

N-(3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1677**),

N-(3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1678**),

N-(3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1679**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1680**),

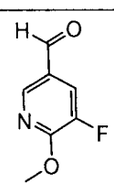
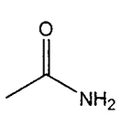
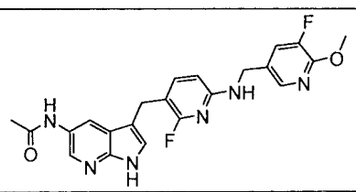
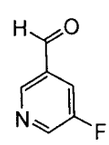
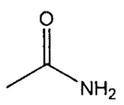
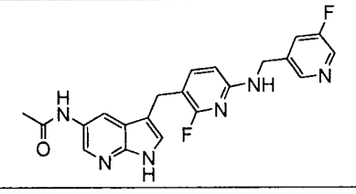
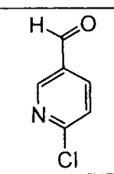
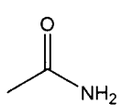
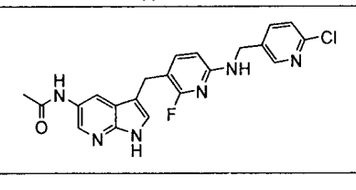
N-(3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1681**),

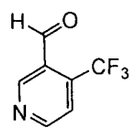
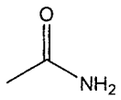
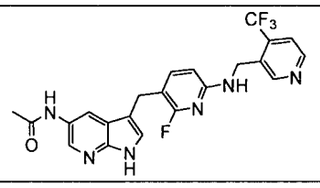
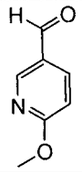
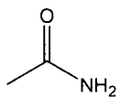
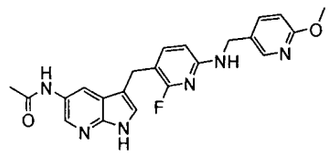
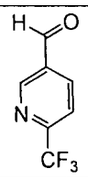
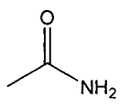
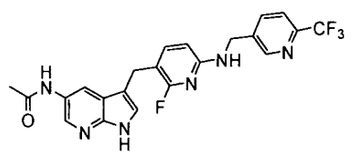
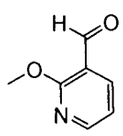
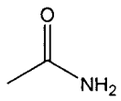
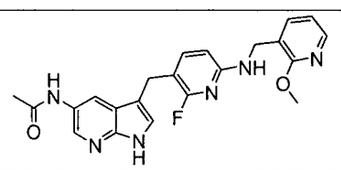
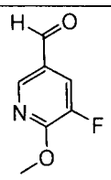
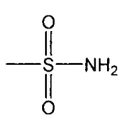
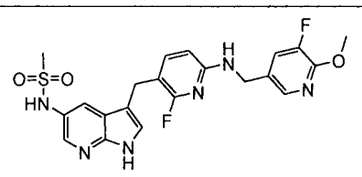
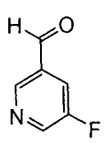
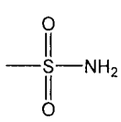
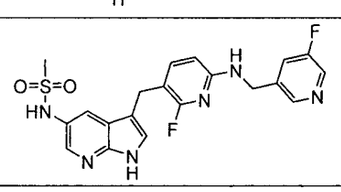
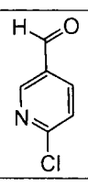
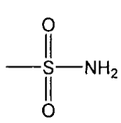
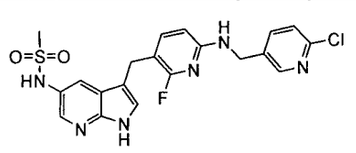
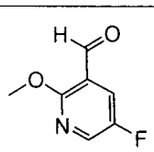
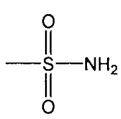
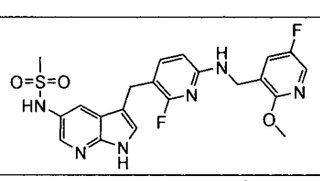
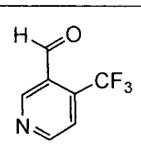
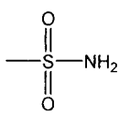
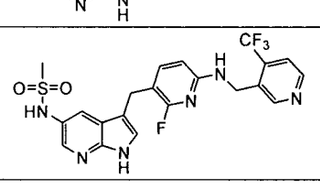
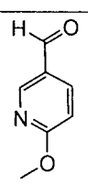
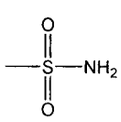
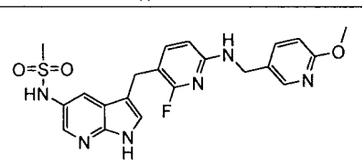
N-(3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1682**),

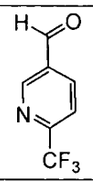
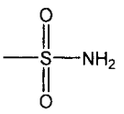
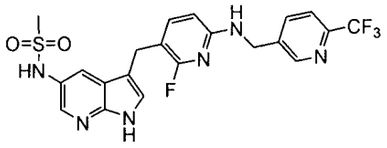
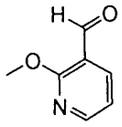
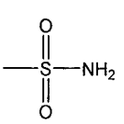
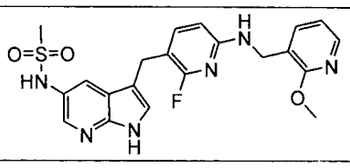
N-(3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1683**), y

N-(3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1684**).

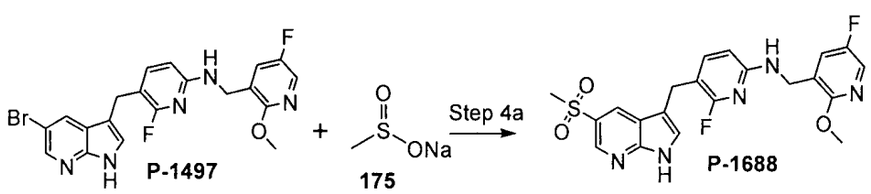
La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 3 y acetamida o metanosulfonamida (columna 3) usado en la etapa 4 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

Número de compuesto	Aldehído	Etapa 4	Compuesto	MS (ESI) $[M+H^+]^+$
P-1670				
P-1671				
P-1672				

P-1673				
P-1674				
P-1675				
P-1676				
P-1677				
P-1678				
P-1679				
P-1680				
P-1681				
P-1682				

P-1683				
P-1684				

[0421] [6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina **P-1688** se prepara a partir de [5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina **P-1497** por la siguiente etapa 4a.

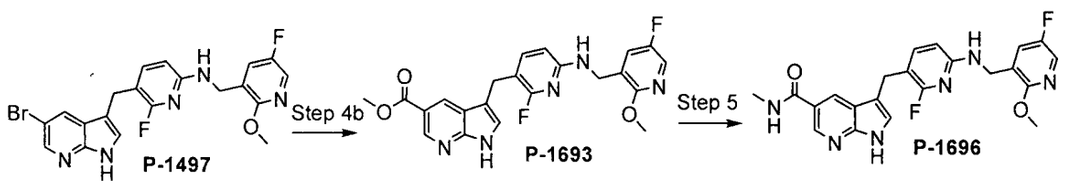


*Etapa 4a – Preparación de [6-fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1688**):*

[0422] [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1497**, 1 equivalente) se disolvió en 5 ml de sulfóxido de dimetilo en un vial que puede sellarse. Yoduro de cobre(I) (0.2 equivalente), L-prolina (0.2 equivalente), metanosulfinato de sodio (**175**, 1.2 equivalentes), e hidróxido de sodio (0.2 equivalente) se agregan. El vial se selló y se calentó a 100 °C durante la noche, luego yoduro de cobre(I) adicional (0.2 equivalente), L-prolina (0.2 equivalente), metanosulfinato de sodio (1.2 equivalente), e hidróxido de sodio (0.2 equivalente) se agregan, y la reacción se selló y se calentó a 120 °C durante la noche. La reacción se agregó a acetato de etilo y salmuera y se extrajo. La capa orgánica se concentró bajo vacío y el material resultante se disolvió en tetrahidrofurano para purificación en una columna C18 de fase inversa, eluyendo con 0-100% de metanol (con 10% tetrahidrofurano)/agua. Las fracciones apropiadas se combinan y concentran bajo vacío. El material resultante se trituró con metil ter-butil éter y se filtró, lavando con metil ter-butil éter, luego heptano. El sólido se secó bajo vacío para proporcionar el compuesto deseado.

[0423] Metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico **P-1696** se prepara a partir de [5-(5-bromo-1H-

pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina **P-1497** por las siguientes etapas 4b y 5.



*Etapa 4b – Preparación de metiléster del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1693**):*

[0424] En un bomba calorimétrica Parr de 2 L, [5-(5-bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1497**, 1 equivalente), trietilamina (2 equivalentes), y [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II) (0.03 equivalentes) se combinan con 300 ml de metanol. La reacción se calentó a 100 °C bajo 100 psi de monóxido de carbono durante la noche. La mezcla de reacción se concentró bajo vacío, se recogió en acetato de etilo y se lavó con agua. La capa orgánica se concentró bajo vacío, el residuo se disolvió en diclorometano y se purificó por cromatografía de columna en gel de sílice, eluyendo con 0-10% de metanol en diclorometano. Las fracciones apropiadas se combinan y concentran bajo vacío para proporcionar el compuesto deseado.

*Etapa 5 – Preparación de metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1696**):*

[0425] Metiléster del ácido 3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1693**, 1 equivalente) se suspendió con metilamina (2N en metanol, 15 equivalentes) en un vial que puede sellarse, se selló y se calentó a 50 °C durante la noche. Metilamina adicional (2N en metanol, 15 equivalentes) se agregó y se calentó a 50 °C durante la noche. La reacción se concentró bajo vacío, el residuo se disolvió en tetrahidrofurano para purificación en una columna C18 de fase inversa, eluyendo con 0-100% de metanol (con 10% tetrahidrofurano)/agua. Las fracciones apropiadas se combinan y concentran bajo vacío. El material resultante se trituró con acetato de etilo/heptano y se filtró, lavando con heptano. El sólido se secó bajo vacío para proporcionar el compuesto deseado.

[0426] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 24, usando las etapas 4a o etapas 4b y etapa 5, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan reemplazando opcionalmente 5-fluoro-2-

metoxi-piridin-3-carbaldehído **37**, con un aldehído adecuado en la etapa 3. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1685**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1686**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1687**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1689**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1690**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1691**),

[6-Fluoro-5-(5-metanosulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1692**),

metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1694**),

metilamida del ácido 3-{2-Fluoro-6-[(5-fluoro-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1695**),

metilamida del ácido 3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1697**),

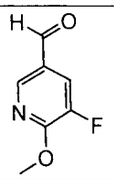
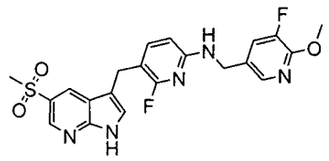
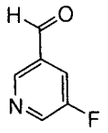
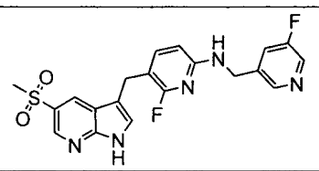
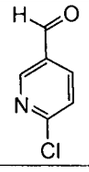
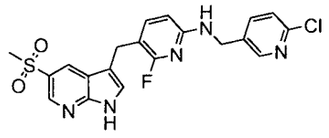
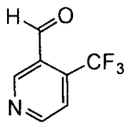
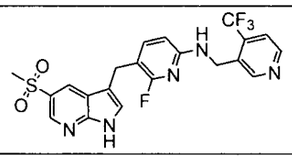
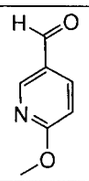
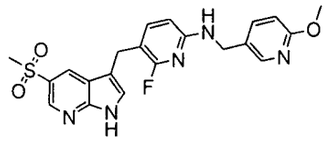
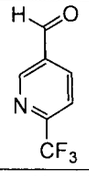
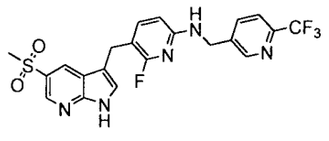
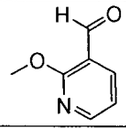
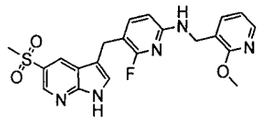
metilamida del ácido 3-{2-Fluoro-6-[(4-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1698**),

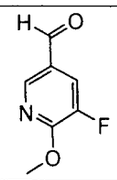
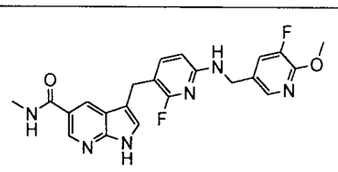
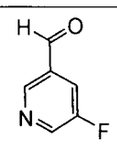
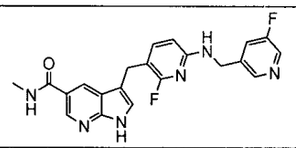
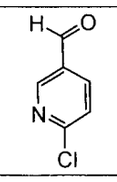
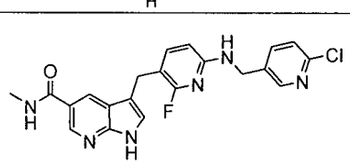
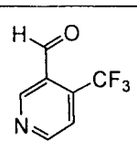
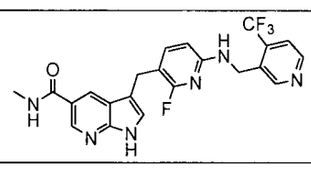
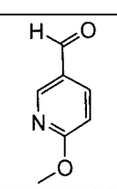
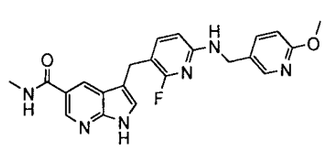
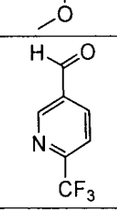
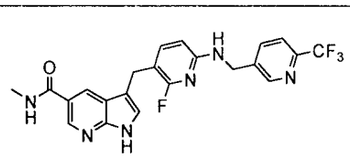
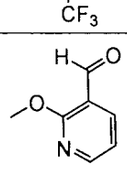
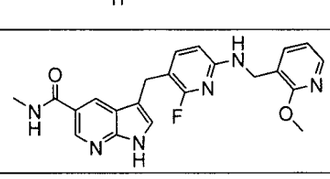
metilamida del ácido 3-{2-Fluoro-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1699**),

metilamida del ácido 3-{2-Fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1700**), y

metilamida del ácido 3-{2-Fluoro-6-[(2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carboxílico (**P-1701**).

La siguiente tabla indica el compuesto aldehído (columna 2) usado en la etapa 3 y, si se usa la etapa 4a o etapa 4b/5 (columna 3), usado en la etapa 4 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

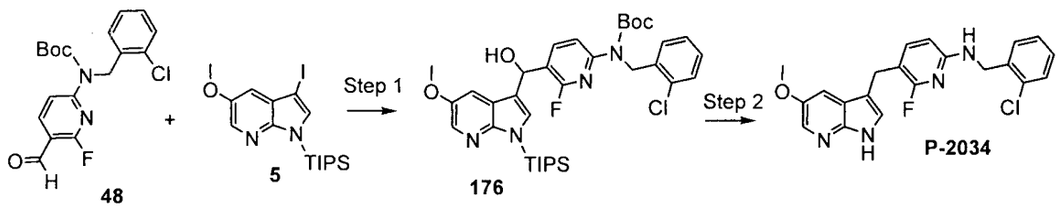
Número de compuesto	Aldehído	Usado en las Etapas	Compuesto	MS (ESI) $[M+H^+]^+$
P-1685		4a		
P-1686		4a		
P-1687		4a		
P-1689		4a		
P-1690		4a		
P-1691		4a		
P-1692		4a		

P-1694		4b/5		
P-1695		4b/5		
P-1697		4b/5		
P-1698		4b/5		
P-1699		4b/5		
P-1700		4b/5		
P-1701		4b/5		

Ejemplo 25: Síntesis de (2-cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-2034.

[0427] (2-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-2034** se preparó en dos etapas a partir de ter-butiléster del ácido (2-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico **48** y 3-yodo-5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **5** como se muestra en el Esquema 25.

Esquema 25



*Etapa 1 – Preparación de ter-butiléster del ácido (2-cloro-bencil)-{6-fluoro-5-[hidroxi-(5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il}-carbámico (**176**):*

[0428] A 3-yodo-5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**5**, 0.49 g, 1.14 mmol) en 6.8 ml de tetrahidrofurano a -50 °C bajo nitrógeno, cloruro de isopropilmagnesio (0.569 ml, 2.0 M en tetrahidrofurano, 1.14 mmol) se agregó lentamente. La reacción se dejó calentar a 5 °C durante 70 minutos, luego se enfrió a -60 °C y ter-butiléster del ácido (2-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico (**48**, 0.23 g, 0.63 mmol) en 30.0 ml de tetrahidrofurano se agregó. La reacción se dejó calentar a temperatura ambiente durante 1 hora, luego se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**176**, 0.400 g). MS (ESI) $[M+H^+]^+ = 669.4$.

*Etapa 2 – Preparación de (2-cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2034**):*

[0429] A ter-butiléster del ácido (2-cloro-bencil)-{6-fluoro-5-[hidroxi-(5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il}-carbámico (**176**, 400 mg, 0.598 mmol) en 20.0 ml de diclorometano, trietilsilano (2.00 ml, 12.5 mmol) y ácido trifluoroacético (1.00 ml, 13.0 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 4 horas, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo vacío. El material resultante se purificó por cromatografía de columna en gel de sílice eluyendo con 20-100% de acetato de etilo en hexano. Las fracciones apropiadas se combinaron y los solventes se removieron bajo vacío para proporcionar el compuesto deseado como un sólido blanco (**P-2034**, 60.7 mg). MS (ESI) $[M+H^+]^+ = 397.1$.

[0430] Compuestos adicionales se preparan siguiendo el protocolo del Esquema 25, donde las condiciones pueden variar, por ejemplo, cualquiera de los solventes, tiempos de reacción, reactivos, temperaturas, condiciones de desarrollo, u otros parámetros de reacción pueden variarse empleando solventes alternos, reactivos, tiempos de reacción, temperaturas, condiciones de desarrollo, y similares, cuando se encuentren fácilmente disponibles para un experto en la técnica. Los compuestos se preparan usando una 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina adecuada en lugar de 3-

yodo-5-metoxi-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **5** y aldehído adecuado en lugar de ter-butiléster del ácido (2-Cloro-bencil)-(6-fluoro-5-formil-piridin-2-il)-carbámico **48** en la etapa 1. Los siguientes compuestos se elaboran usando este procedimiento. Los compuestos en la siguiente tabla se caracterizaron por espectroscopía de NMR con ^{1}H y ^{13}C así como espectrometría de masas.

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1499**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1500**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1501**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1513**),

(5-Fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1514**),

(6-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1515**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1516**),

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1517**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1518**),

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1519**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1520**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-1521**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1522**),

(6-Cloro-piridin-3-ilmetil)-[4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1523**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-1524**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1525**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1526**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1527**),

(6-Metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1532**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1533**),

(5-Fluoro-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1534**),

(6-Cloro-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1535**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1536**),

[6-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1537**),

[6-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1538**),

(2-Metoxi-piridin-3-ilmetil)-[6-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1539**),

(6-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1554**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1555**),

(5-Fluoro-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1556**),

(6-Cloro-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1557**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1558**),

[3-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1559**),

[3-Metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1560**),

(2-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1561**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1562**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1563**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1564**),

(6-Cloro-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1565**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[3-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1566**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1567**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1568**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1579**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1580**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-1581**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1582**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1597**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1598**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina (**P-1607**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1608**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1609**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1630**),

(5-Fluoro-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1631**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1632**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-1633**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1634**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1635**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1636**),

[5-(5-Fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1637**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-1727**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1728**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1729**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-1730**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1731**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1732**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-amina (**P-1733**),

[6-Fluoro-5-(4-metil-7H-pirrolo[2,3-d]pirimidin-5-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-1734**),

(2-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2035**),

(2-Cloro-bencil)-[5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2036**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2040**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2042**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2043**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2044**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2045**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2047**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2050**),

(2-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2051**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2052**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[(S)-1-(4-fluoro-fenil)-etil]-amina (**P-2058**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2062**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2063**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2064**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-4-ilmetil)-amina (**P-2065**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2067**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2070**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2071**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2072**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2073**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2075**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2135**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2136**),

[3-Metoxi-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2143**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2144**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2145**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2146**),

[3-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2147**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2152**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2153**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2154**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2155**),

3-{[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-ilamino]-metil}-5-fluoro-1-metil-1H-piridin-2-ona (**P-2157**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2158**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2159**),

(6-Metoxi-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-2162**),

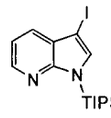
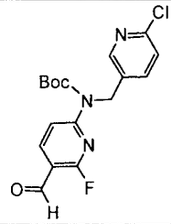
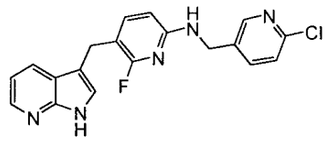
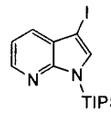
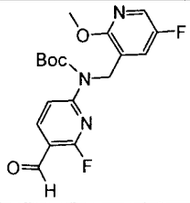
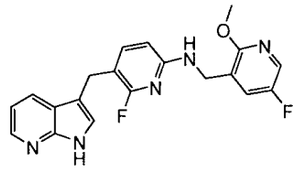
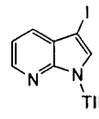
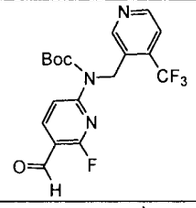
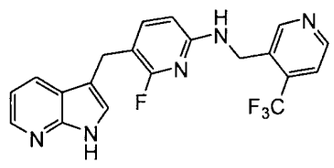
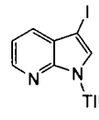
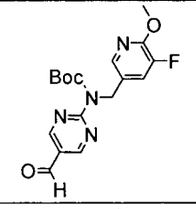
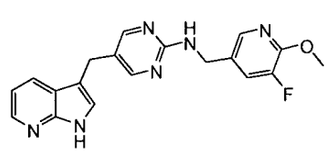
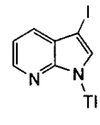
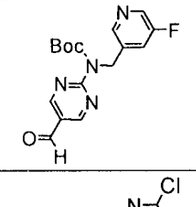
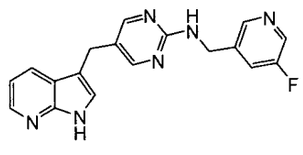
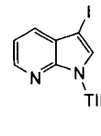
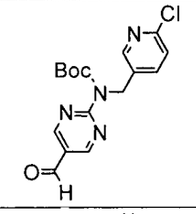
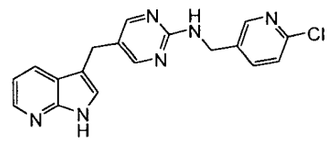
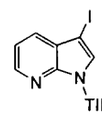
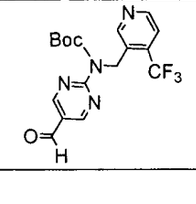
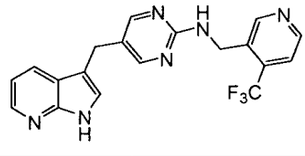
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina (**P-2163**),

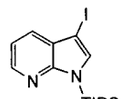
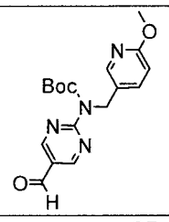
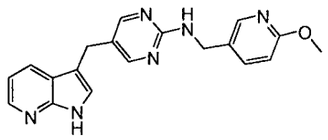
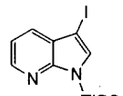
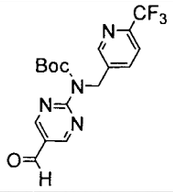
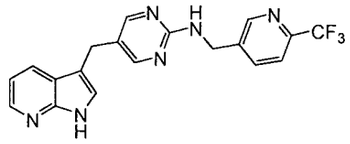
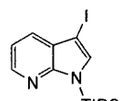
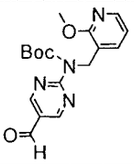
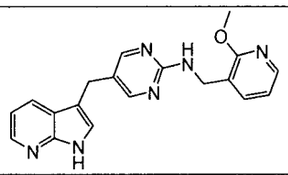
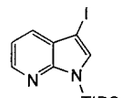
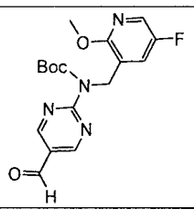
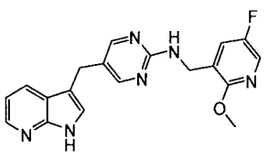
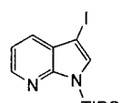
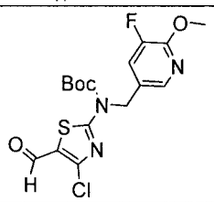
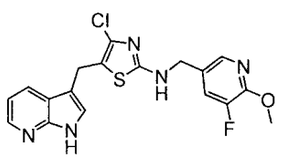
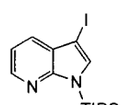
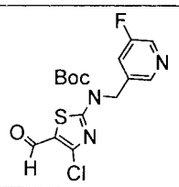
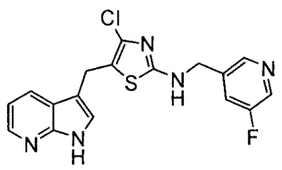
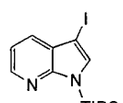
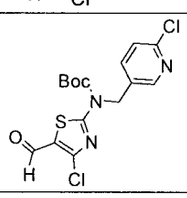
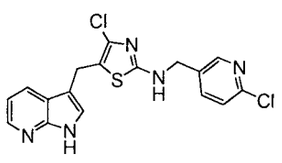
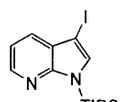
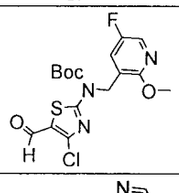
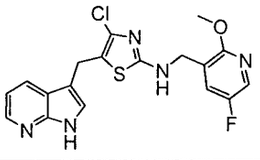
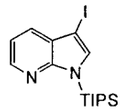
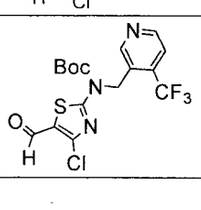
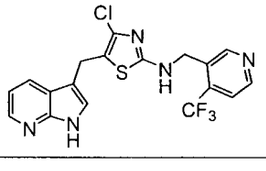
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-2164**),

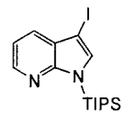
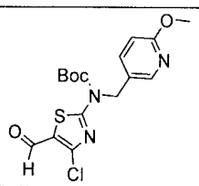
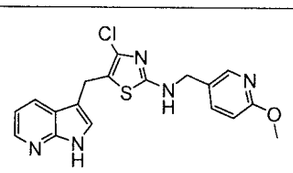
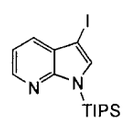
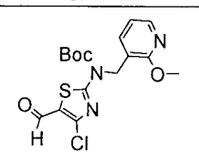
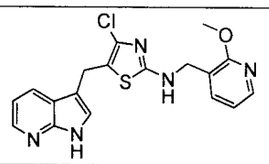
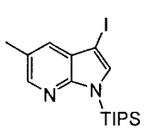
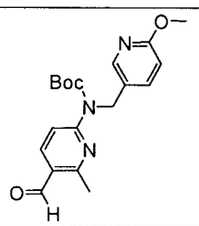
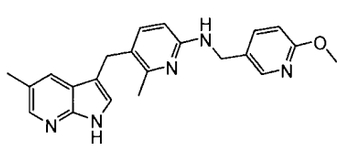
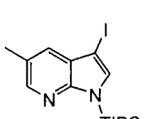
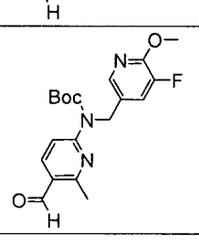
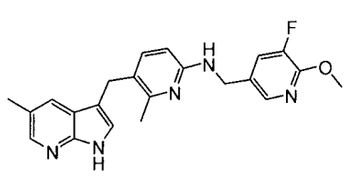
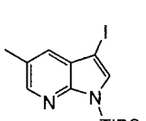
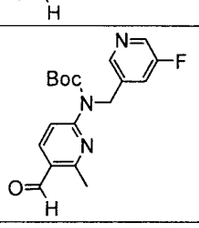
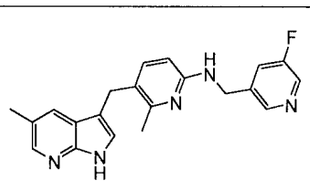
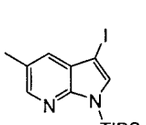
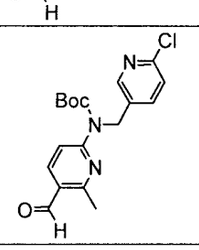
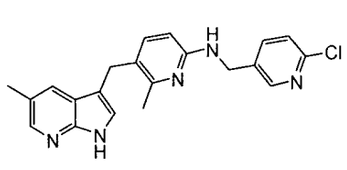
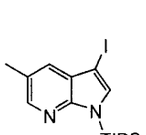
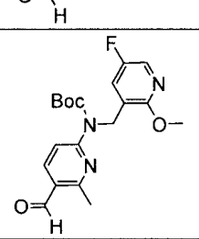
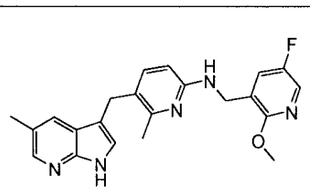
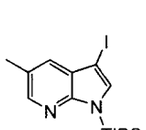
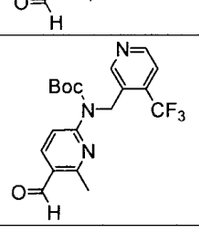
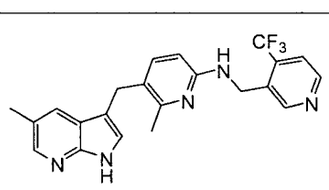
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**), y

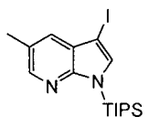
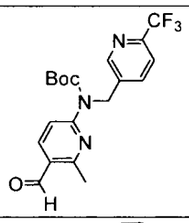
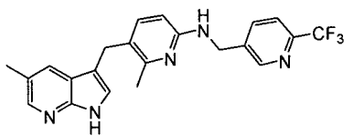
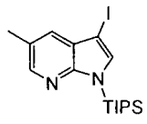
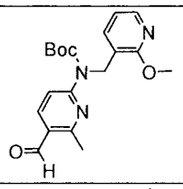
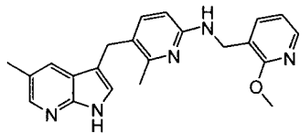
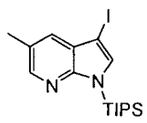
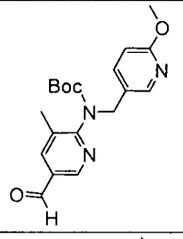
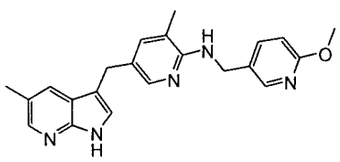
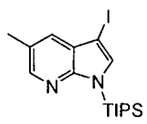
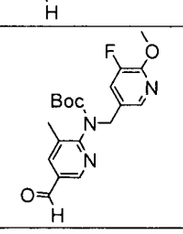
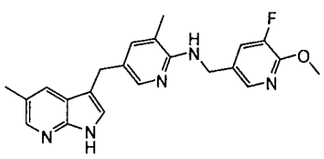
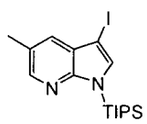
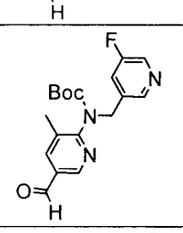
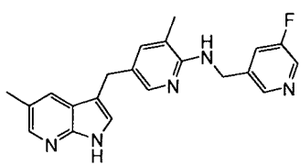
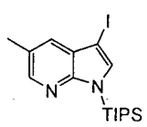
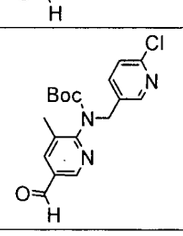
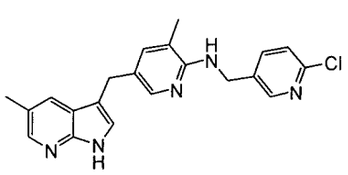
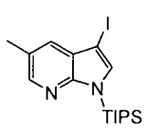
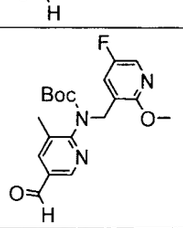
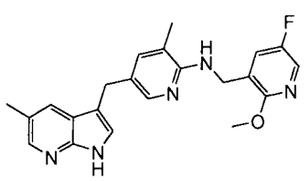
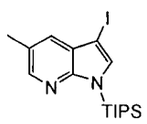
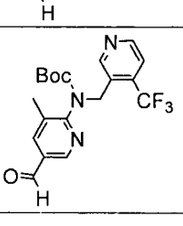
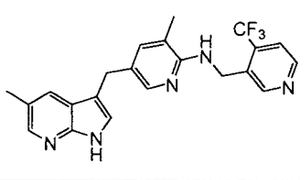
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2172**).

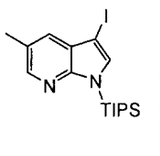
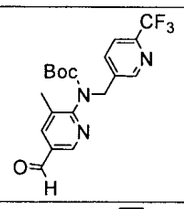
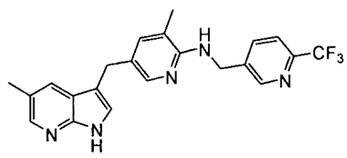
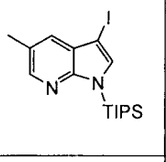
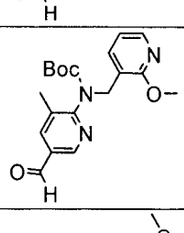
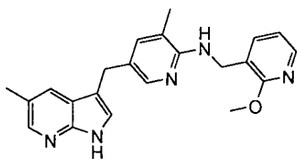
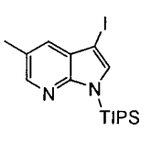
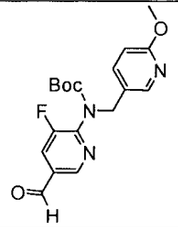
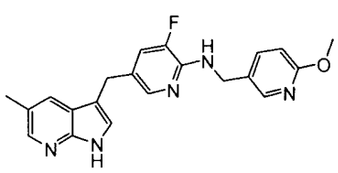
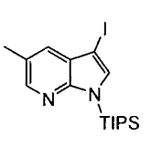
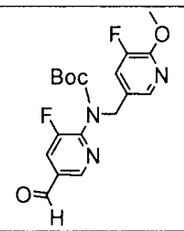
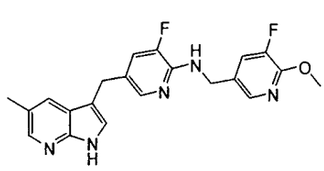
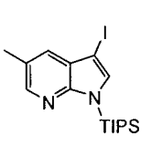
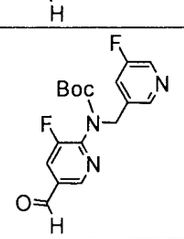
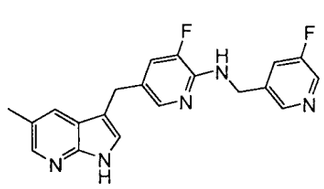
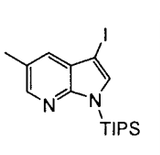
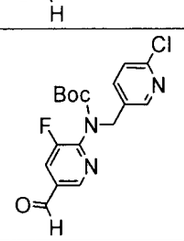
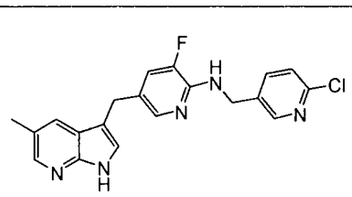
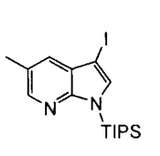
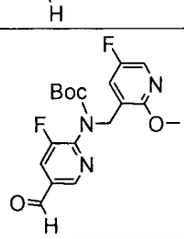
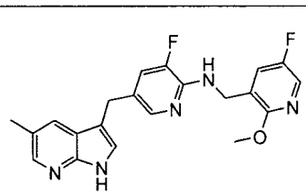
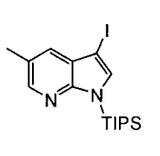
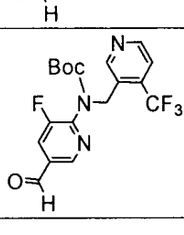
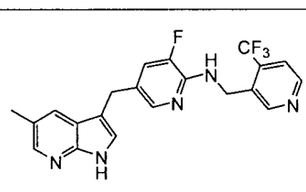
La siguiente tabla indica el compuesto 1H-pirrolo[2,3-b]piridina (columna 2) y el compuesto aldehído (columna 3) usado en la etapa 1 para proporcionar el compuesto deseado (columna 4). El número de compuesto se proporciona en la columna 1, y la masa observada está en la columna 5.

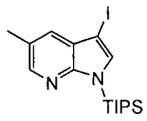
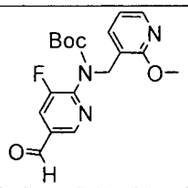
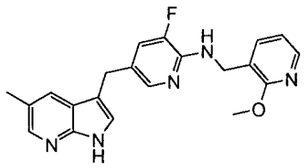
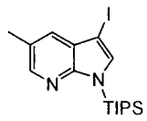
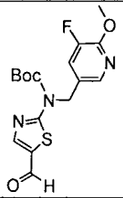
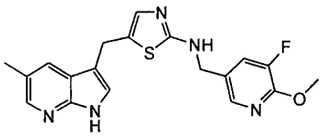
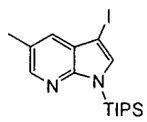
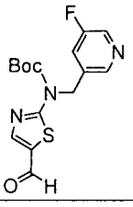
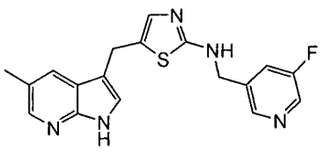
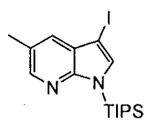
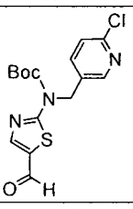
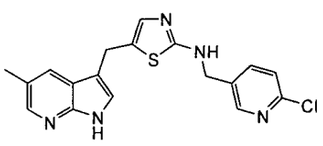
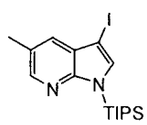
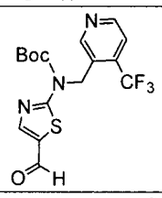
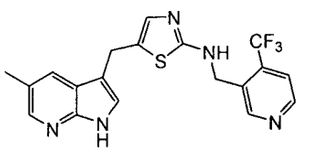
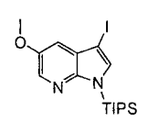
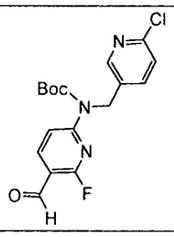
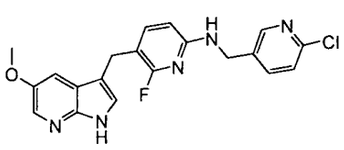
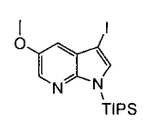
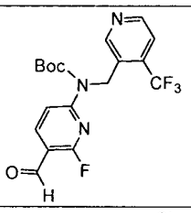
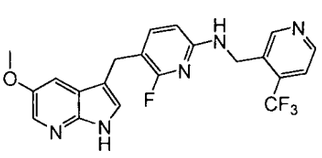
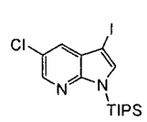
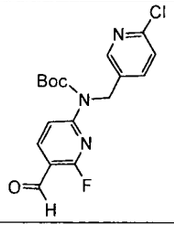
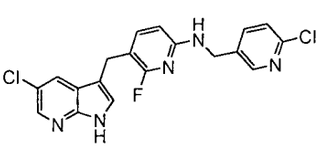
Número de comp.	1H-pirrolo[2,3-b]piridina	Aldehído	Estructura del compuesto	MS (ESI) $[M+H^+]^+$
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P-1500				
P-1501				
P-1513				
P-1514				
P-1515				
P-1516				

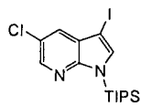
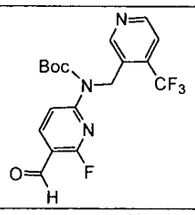
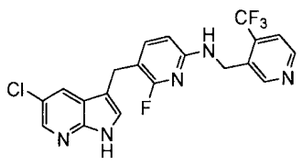
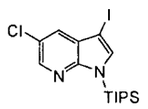
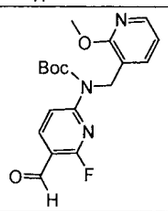
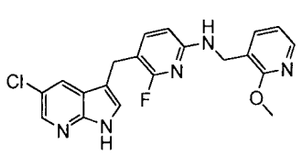
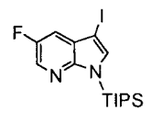
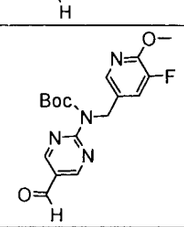
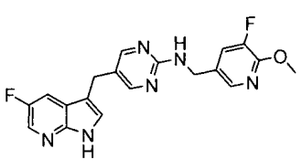
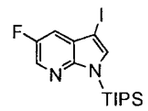
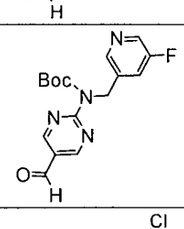
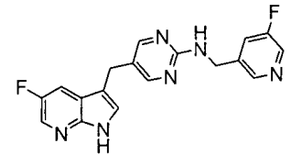
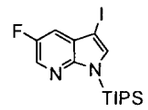
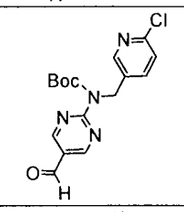
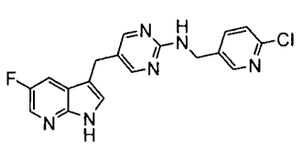
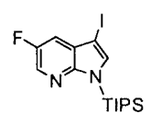
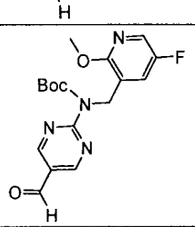
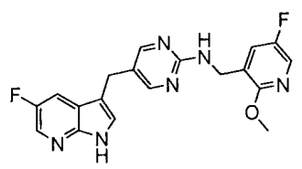
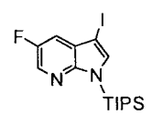
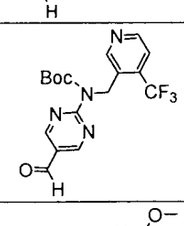
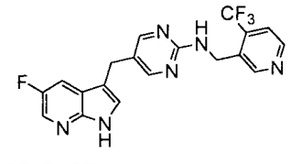
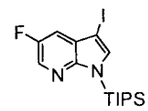
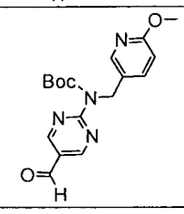
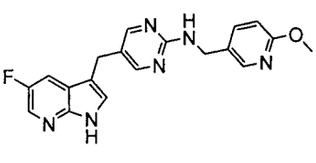
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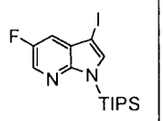
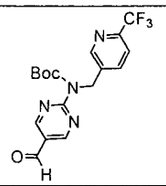
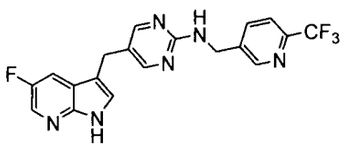
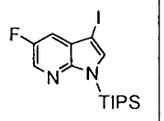
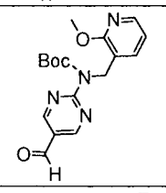
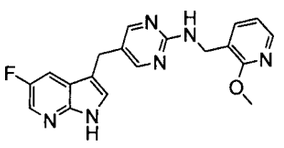
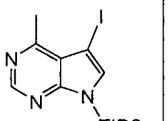
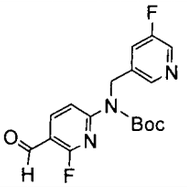
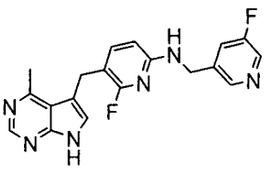
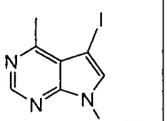
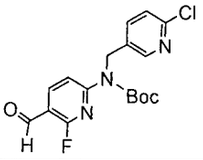
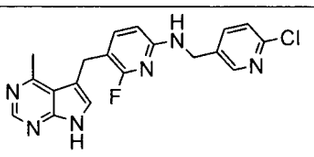
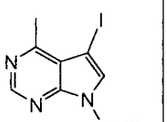
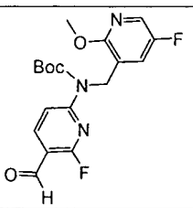
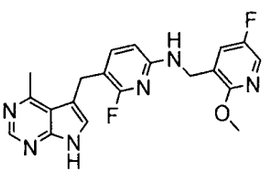
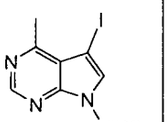
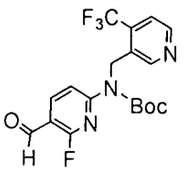
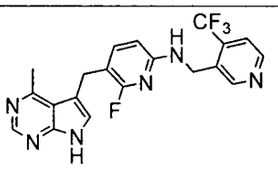
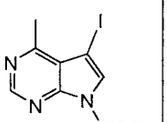
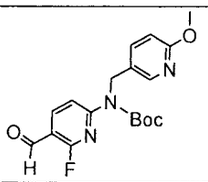
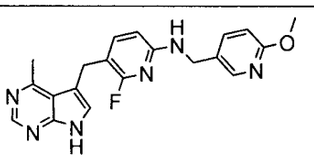
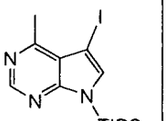
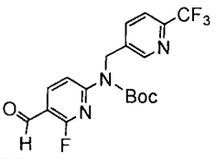
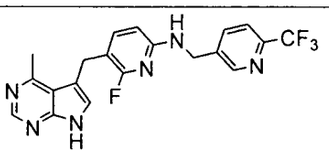
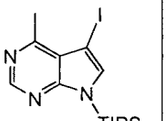
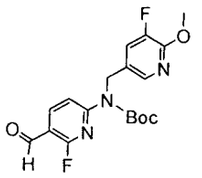
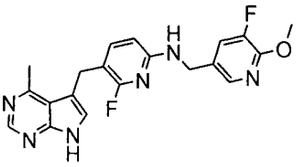
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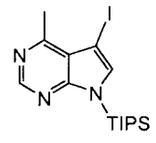
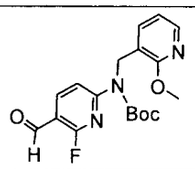
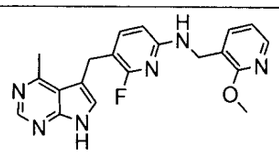
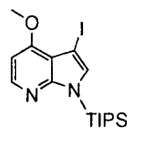
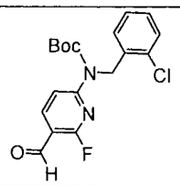
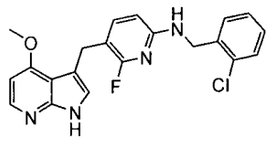
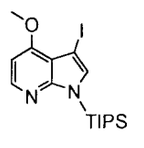
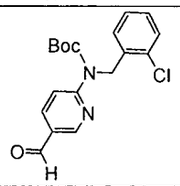
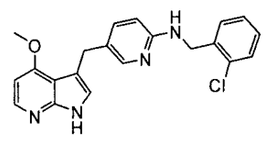
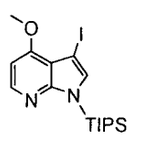
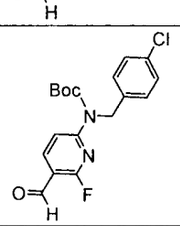
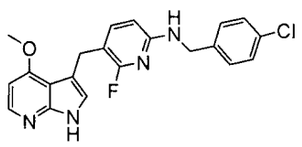
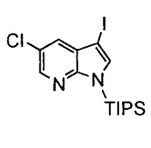
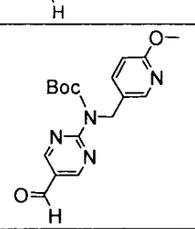
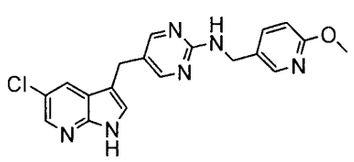
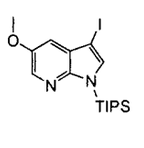
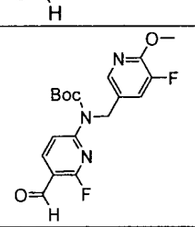
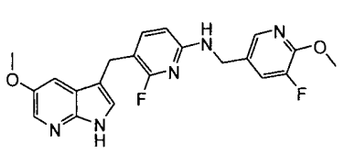
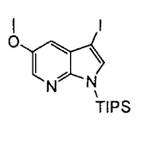
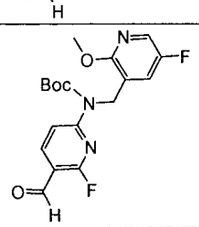
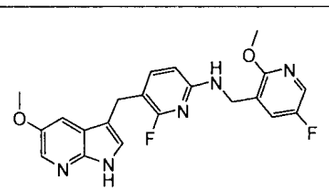
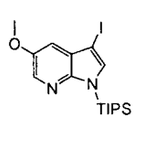
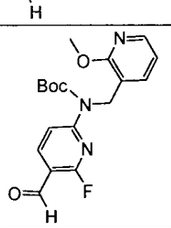
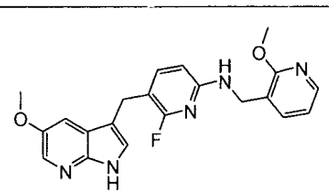
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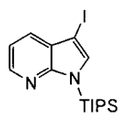
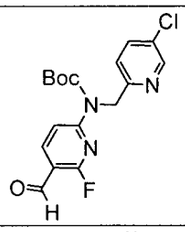
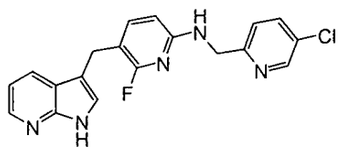
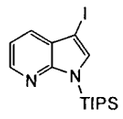
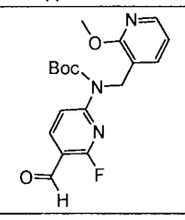
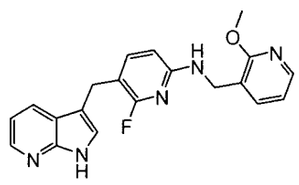
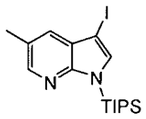
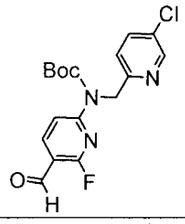
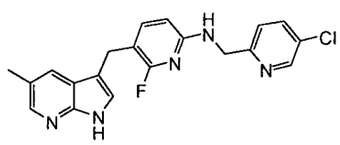
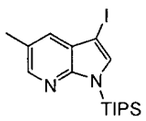
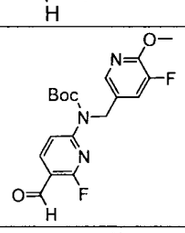
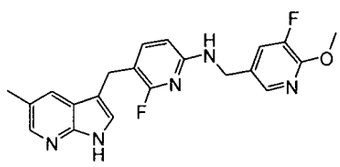
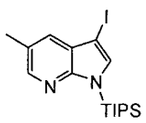
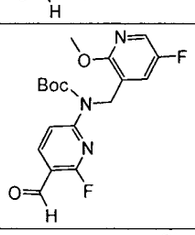
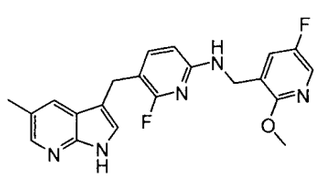
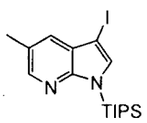
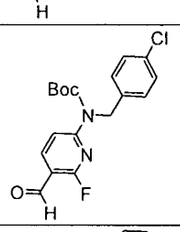
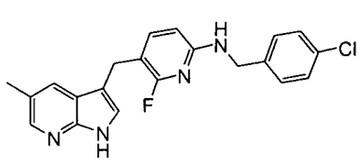
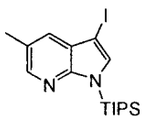
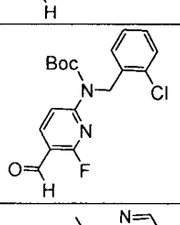
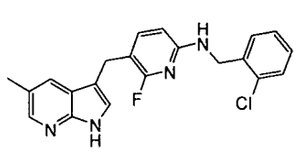
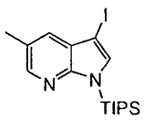
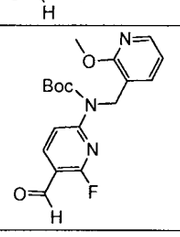
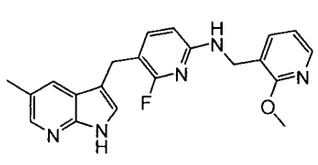
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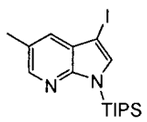
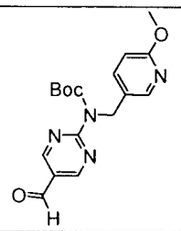
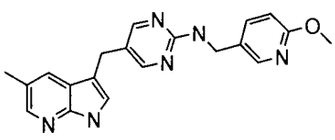
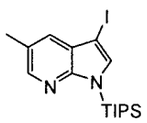
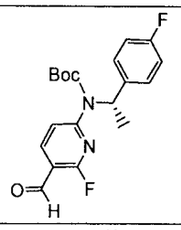
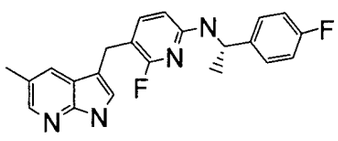
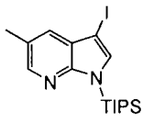
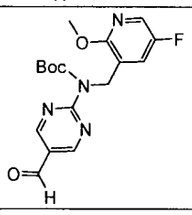
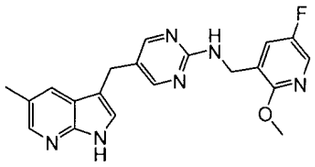
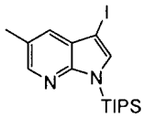
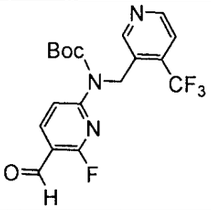
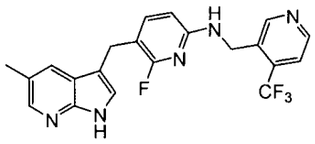
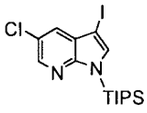
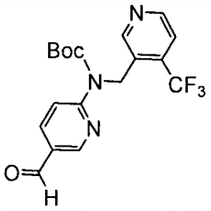
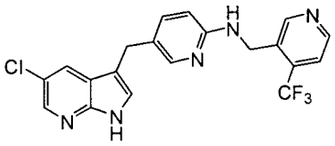
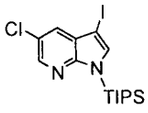
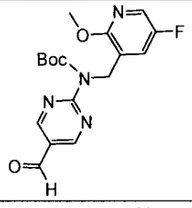
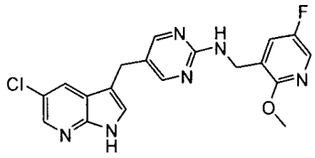
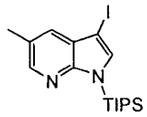
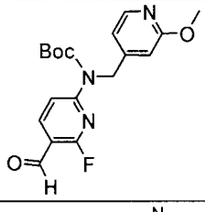
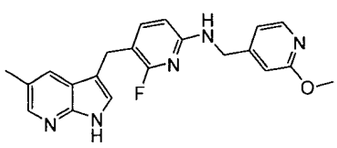
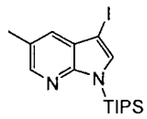
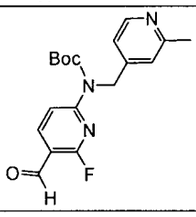
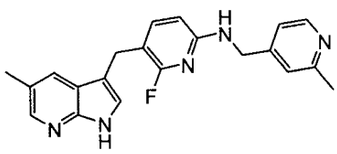
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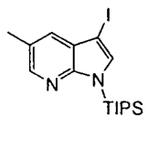
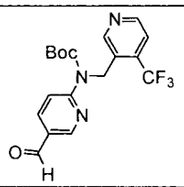
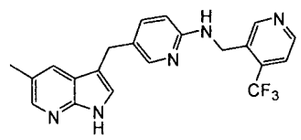
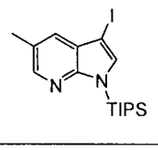
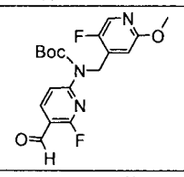
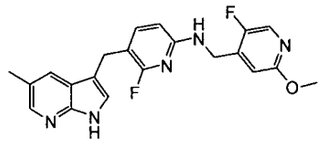
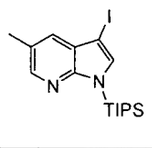
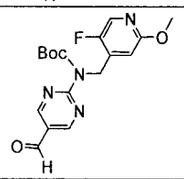
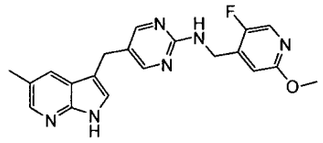
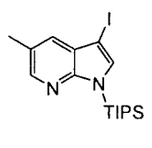
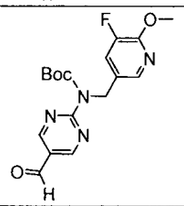
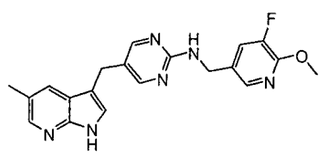
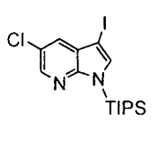
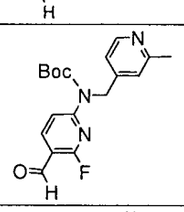
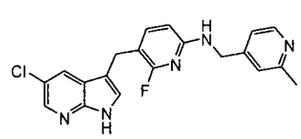
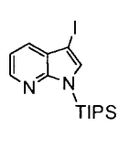
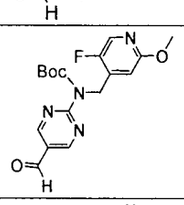
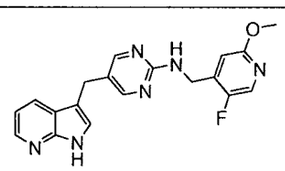
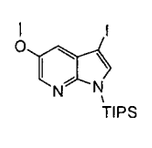
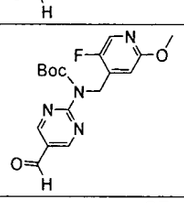
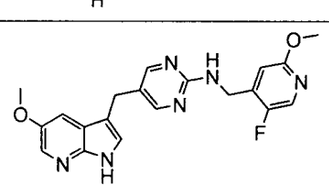
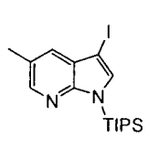
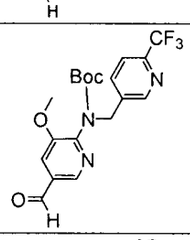
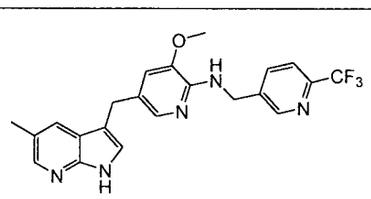
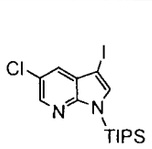
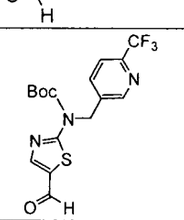
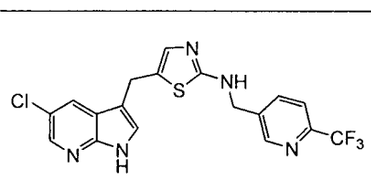
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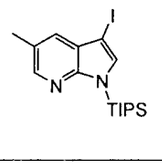
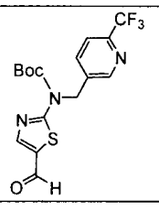
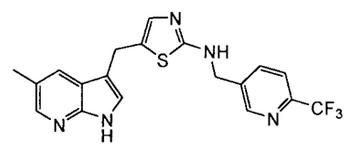
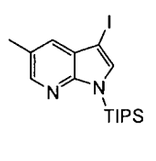
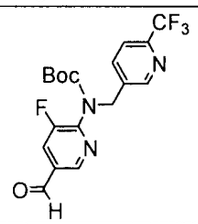
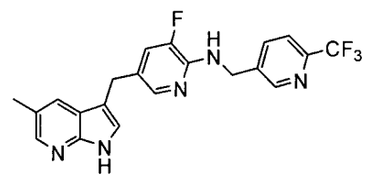
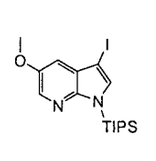
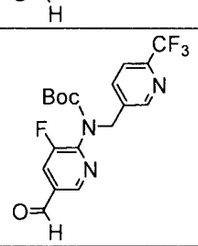
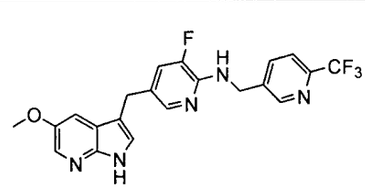
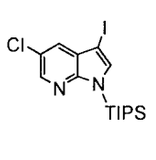
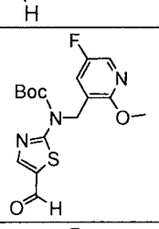
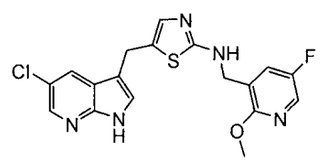
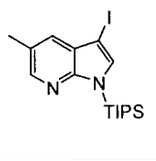
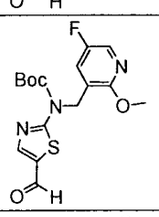
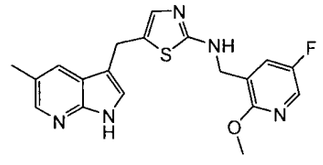
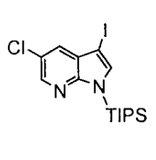
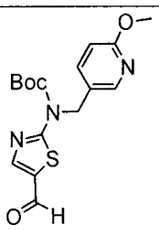
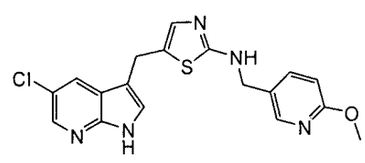
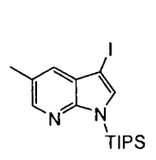
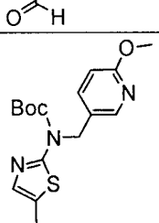
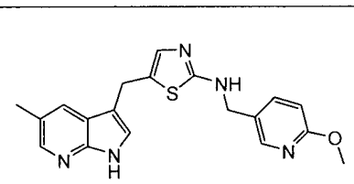
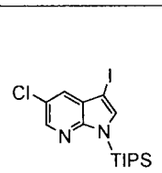
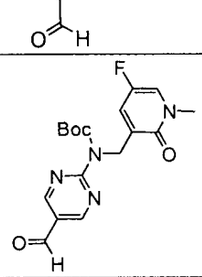
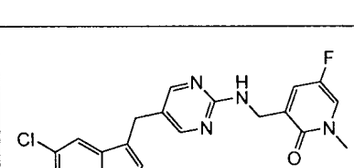
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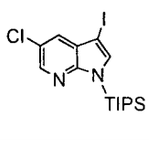
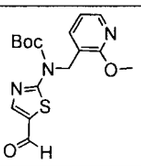
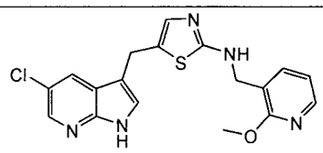
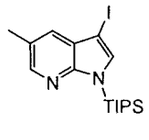
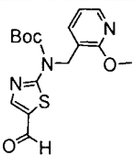
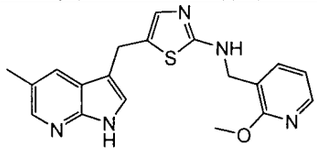
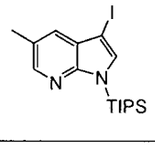
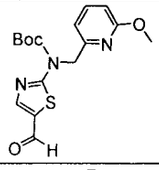
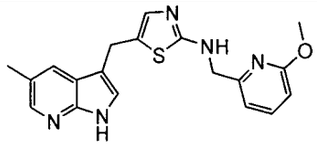
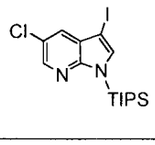
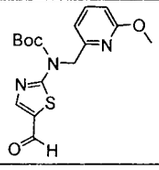
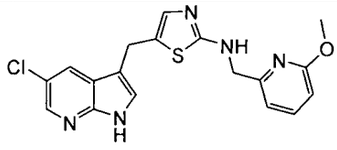
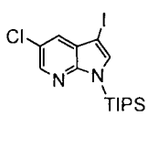
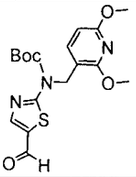
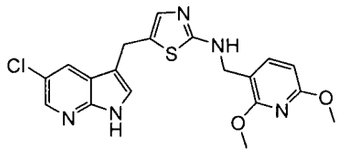
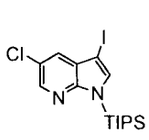
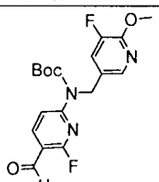
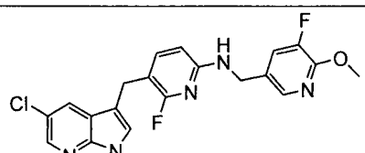
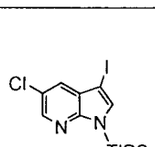
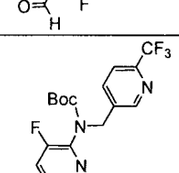
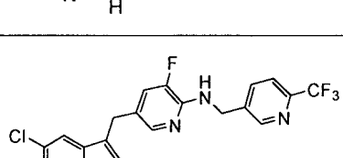
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P-2051				
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P-2144				

P-2145				
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Ejempló 26: Formas y formulaciones de los compuestos

[0431] Los compuestos dados a conocer en este documento pueden prepararse en formas adicionales, tales como polimorfos, formas salinas y complejos. Tales formas sólidas además pueden mejorar las propiedades biofarmacéuticas, y pueden además formularse para aumentar las propiedades biofarmacéuticas. Por ejemplo, los compuestos de la invención forman sales de adición de ácido tales como sales clorhidrato o tosilato, o forman un complejo con ácidos polipróticos, tal como ácido cítrico, preferentemente en donde el complejo es sustancialmente amorfo. Tal complejo amorfo también puede procesarse con la adición de un polímero, tal como HPMCAS, que estabiliza además la

forma amorfa. El proceso también puede incluir secado por aspersión del material. El compuesto se disuelve en 400-500 ml de acetona y se agrega con agitación y calor a 1 equivalente de ácido cítrico disuelto en etanol. La solución se seca por aspersión para proporcionar el complejo seco. Material adicional se formula con la adición del complejo compuesto/citrato al polímero en la misma relación de acetona/etanol, por ejemplo, usando HPMCAS o una mezcla de Eudragit® L100-55 y Poloxámero 407. En una muestra, los componentes se combinan en las relaciones de peso de 40-50% de compuesto, 15-25% de ácido cítrico, 25-35% de Eudragit® L100-55 y 1-10% de Poloxámero 407. En una muestra, los componentes se combinan en las relaciones de peso de 40-50% de compuesto, 15-25% de ácido cítrico, y 30-40% de HPMCAS. La naturaleza amorfa del complejo o formulación del complejo resultante puede determinarse por Difracción en Polvo de Rayos X (XRPD), espectrometría infrarroja, y calorimetría diferencial de barrido. Por ejemplo, usando un difractómetro en polvo de rayos X ShimadzuXRD-6000 usando radiación Cu Kα. El voltaje y amperaje del tubo se ajustan a 40 kV y 40 mA, respectivamente. Los orificios de divergencia y dispersión se ajustan a 1° y el orificio receptor se ajusta a 0.15 mm. La radiación difractada se detecta por un detector de centelleo de NaI. Se usó una exploración continua θ-2θ a 3 °/min (0.4 s/etapa de 0.02°) de 2.5 a 40 °2θ. Se analiza un estándar de silicio para verificar la alineación del instrumento. Los datos se recolectan y analizan usando XRD-6100/7000 v. 5.0. La muestra se prepara para análisis al colocarla en un soporte de aluminio con inserción de silicio. La DSC se usa para demostrar que los complejos carecen de una transición característica y se han fundido completamente antes de cualquier transición cristalina de base libre, lo que soporta además que estos complejos son amorfos.

Ejemplo 27: Propiedades de los compuestos

[0432] Aunque la actividad inhibitoria de los compuestos sobre cualquiera de las cinasas Fms, Flt-3 y Kit es importante para su actividad para el tratamiento de una enfermedad, los compuestos descritos en este documento muestran propiedades favorables que proporcionan ventajas como fármacos también. En algunos casos, la selectividad de Fms en relación con Kit y otras cinasas proporciona la actividad preferida para tratar ciertas enfermedades, tales como artritis reumatoide, enfermedad de Alzheimer, enfermedad de Parkinson, osteoartritis, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, o hipertrofia renal. En algunos casos, la selectividad por Fms de los compuestos en combinación con la incapacidad de los compuestos para cruzar la barrera hematoencefálica proporciona una actividad preferida para tratar ciertas enfermedades, tales como osteoartritis, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, o hipertrofia renal. En algunos casos, la selectividad por Fms de los compuestos en combinación con la capacidad de los compuestos para cruzar con efectividad la barrera hematoencefálica proporciona una actividad preferida para tratar ciertas enfermedades, tales como artritis reumatoide, enfermedad de Alzheimer o enfermedad de Parkinson. En algunos casos, la

actividad dual Fms/Kit proporciona una actividad preferida para tratar ciertas enfermedades, tales como cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide, o esclerosis múltiple. En algunos casos, la actividad dual Fms/Flt-3 proporciona una actividad preferida para tratar ciertas enfermedades, tal como leucemia mieloide aguda. Además de demostrar una actividad inhibitoria de cinasas contra Fms, Kit, Flt-3 o al menos tanto Fms como Kit, o al menos tanto Fms como Flt-3 en ensayos bioquímicos y basados en células, los compuestos tienen una solubilidad mejorada, propiedades farmacocinéticas mejoradas, y baja inhibición de Cyp. Los compuestos se valoran en los siguientes ensayos o ensayos similares disponibles para u experto en la técnica.

[0433] Los ensayos para actividad bioquímico y basada en células se conocen en la técnica, por ejemplo, Publicación de Solicitud de Patente de E. U. Número 2009/0076046, cuya descripción se incorpora por la presente para referencia dado que se relaciona con tales ensayos. En un ensayo, los valores IC_{50} de la actividad bioquímica se determinan con respecto a la inhibición de la actividad de cinasa c-Kit, donde la inhibición de la fosforilación de un sustrato peptídico se mide como una función de la concentración del compuesto. Los compuestos que se probarán se disuelven en DMSO a una concentración de 20 mM. Estos se diluyen 30 µl en 120 µl de DMSO (4 mM) y 1 µl se agrega a una placa de ensayo. Estos entonces se diluyen de manera seriada 1:2 (50 µl a 100 µl de DMSO) para un total de 8 puntos. Las placas se preparan de tal modo que cada reacción de cinasa sea de 20 µl en reguladór 1x de cinasa (25 mM HEPES, pH 7.5, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 0.01% de Tween-20, 1 mM DTT, 0.01% de BSA), 5% DMSO y 100 µM ATP. El sustrato es 30 nM biotina-(E4Y)10 (Millipore). La cinasa C-kit (obtenida de Millipore (#14-559) o preparada como se describe en la Publicación de Solicitud de Patente de E. U. Número 2009/0076046, cuya descripción se incorpora por la presente para referencia dado que se relaciona con este ensayo) está a 0.75 ng por muestra. Después de una incubación de la reacción de cinasa durante 1 hora a temperatura ambiente, 5 µl de cuentas donadoras (Cuentas recubiertas con estreptavidina (Perkin Elmer Life Science) concentración final 10 µg/ml) en regulador de detención (25 mM Hepes pH 7.5, 100 mM EDTA, 0.01% BSA) se agregan, la muestra se mezcla e incuba durante 20 minutos a temperatura ambiente antes de agregar 5 µl de cuentas aceptoras (cuentas recubiertas con PY20 (Perkin Elmer Life Science) concentración final 10 µg/ml) en regulador de detención. Las muestras se incuban durante 60 minutos a temperatura ambiente y la señal por pozo se lee en un lector Envision. El sustrato fosforilado resulta en la unión del anticuerpo PY20 y la asociación de las cuentas donadoras y aceptoras, de tal modo que la señal se correlaciona con actividad de cinasa. La señal versus concentración de compuesto se usa para determinar la IC_{50}.

[0434] En un ensayo, los valores IC_{50} de la actividad bioquímica se determinan con respecto a la inhibición de la actividad de cinasa Fms, donde la inhibición de la fosforilación de un sustrato peptídico se mide como una función de la concentración del compuesto. Los compuestos que se probarán, disueltos en DMSO (1 µl), se agregan a una placa blanca de 384 pozos (Costar #3705). Soluciones de trabajo de cinasa Fms (Invitrogen #PV3249), biotina-$(E4Y)_{10}$ sustrato (Upstate Biotech, Cat# 12-440), y ATP (Sigma, Cat#A-3377) se preparan 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 agregan a la placa de 384 pozos para una concentración final de 1 ng/pozo de Fms, 30 nM biotina-$(E4Y)_{10}$ (Upstate Biotechnology) y 100 µM ATP en un volumen de 20 µL. Cada muestra está a 5% de DMSO. La placa se incuba entonces durante 20 minutos a 30 °C. Justo antes de su uso, las soluciones de trabajo de cuentas donadoras y aceptoras del equipo AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M) se preparan en 25 mM Hepes pH 7.5, pH 7.4, 100 mM EDTA, 0.01% de BSA. Para detener la reacción, la placa se descubre en la oscuridad y se agregan 5 µL de solución Donor Beads (cuentas de Estreptavidina) a cada pozo. La placa se incuba a temperatura ambiente durante 20 minutos. Cinco microlitros de solución Acceptor Beads (cuantas recubiertas de PY20) entonces se agregan a cada pozo. La concentración final de cada cuenta es 10 µg/ml. Las placas se incuban a temperatura ambiente durante 60 minutos. La señal de fluorescencia se registra en el lector Envision. El sustrato fosforilado resulta en la unión del anticuerpo PY20 y la asociación de las cuentas donadoras y aceptoras, de tal modo que la señal se correlaciona con actividad de cinasa. La señal versus concentración de compuesto se usa para determinar la IC_{50}.

[0435] En un ensayo, los valores de IC_{50} de la actividad bioquímica se determinan con respecto a la inhibición de la actividad de cinasa Flt-3, donde la inhibición de la fosforilación de un sustrato peptídico se mide como una función de la concentración del compuesto. Los compuestos que se probarán, disueltos en DMSO (1 µl), se agregan a una placa blanca de 384 pozos (Costar #3705). Soluciones de trabajo de cinasa Flt-3 (Invitrogen), biotina-$(E4Y)_{10}$ sustrato (Upstate Biotech, Cat# 12-440), y ATP (Sigma, Cat#A-3377) se preparan en 25 mM Hepes pH 7.5, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 1 mM DTT, y 0.01% de Tween-20. Todos los componentes se agregan a la placa de 384 pozos para una concentración final de 1 ng/pozo de Flt-3, 30 nM biotina-$(E4Y)_{10}$ y 100 µM ATP en un volumen de 20 µL. Cada muestra está a 5% de DMSO. La placa se incuba entonces durante 1 hora a temperatura ambiente. Justo antes de su uso, las soluciones de trabajo de cuentas donadoras y aceptoras del equipo AlphaScreen PY20 Detection Kit (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 descubre en la oscuridad y se agregan 5 µL de solución Donor Beads (cuentas de Estreptavidina) a cada pozo. La placa se incuba a temperatura ambiente durante 20 minutos. Cinco microlitros de solución Acceptor Beads (cuantas recubiertas de PY20) entonces se agregan a cada pozo. La concentración final de cada cuenta es 10 µg/ml. Las placas se incuban a temperatura ambiente

durante 60 minutos. La señal de fluorescencia se registra en el lector Envision. El sustrato fosforilado resulta en la unión del anticuerpo PY20 y la asociación de las cuentas donadoras y aceptoras, de tal modo que la señal se correlaciona con actividad de cinasa. La señal versus concentración de compuesto se usa para determinar la IC_{50}.

[0436] Los compuestos se valoran en una diversidad de ensayos basados en células. Por ejemplo, los ensayos de proliferación en células BCR-FMS/BaF3, BCR-KIT/BaF3, M-NFS-60, M-07e, y BAC1.2F5 se usan para valorar la actividad inhibitoria de Fms o Kit y el ensayo de proliferación en células MV-4-11 se usa para valorar la actividad inhibitoria en Flt-3. Las condiciones de reactivos y del ensayo son como sigue:

Células BCR-FMS/BaF3 y BCR-KIT/BaF3:
Mantenidas en RPMI que contiene 10% de FBS, 1% de PenStrep, 1% de NEAA, y 1% de L-Glutamina, complementado con 1 mg/ml de G418 y 5% de WEHI-CM (o IL-3 recombinante murino).
Las células confluentes se dividen 1:50 a 1:100 cada 3-4 días.

Células M-NFS-60 (ATCC #CRL-1838):
Mantenidas en RPMI que contiene 10% de FBS, 1% de Hepes, 1% de NaPyruvate, y 0.45% de Glucosa, complementado con 62 ng/ml de M-CSF murino.
Las células confluentes se dividen 1:20 cada 3-4 días.

Células M-07e (DSMZ #ACC 104):
Mantenidas en IMDM que contiene 10% de FBS, complementado con 200 ng/ml de SCF humano o 75 ng/µL de SCF (R&D Systems 255-SC).
Las células confluentes se dividen 1:5 a 1:10 cada 3-4 días.

Células BAC1.2F5:
Mantenidas en Alpha-MEM que contiene 10% de Newborn Calf Serum (Invitrogen #26010-074) complementado con 36 ng/ml de M-CSF murino.
Las células confluentes se dividen 1:4 cada 3-4 días.

Células MV-4-11:
Mantenidas en medio Iscove's Modified Dulbecco's Medium que contiene 10% de FBS.
Las células confluentes se dividen 1:4 cada 3-4 días.

En el día 1, las células se cuentan, entonces se centrifugan en un tubo cónico durante 5 minutos a 1000 rpm. El sobrenadante se remueve y las células se re-suspenden como sigue:

BCR-FMS/BaF3 y BCR-KIT/BaF3: resuspendidas en medio de crecimiento + 1 mg/ml G418 (sin WEHI/IL-3) a 2 X 10^5 células/ml.

M-NFS-60: resuspendidas en medio de crecimiento + 62 ng/ml de M-CSF murino a 5 X 10^5 células/ml.

M-07e: resuspendidas en medio de crecimiento + 200 ng/ml de SCF humano a 5 X 10^5 células/ml.

BAC1.2F5: resuspendidas en medio de crecimiento + 36 ng/ml de M-CSF murino a 1.4 X 10^5 células/ml.

MV-4-11: resuspendidas en medio de crecimiento + 10% de FBS a 5 X 10^5 células/ml.

Las células se colocan en placas (50 µL) en cada pozo de una placa de 96 pozos (Corning 3610) y se incuban a 37 °C en 5% CO_2 durante la noche, las células se colocan en placas a una concentración final de células como sigue:

BCR-FMS/BaF3 y BCR-KIT/BaF3: 10,000 células por pozo.

M-NFS-60: 25,000 células por pozo.

M-07e: 25,000 células por pozo.

BAC1.2F5: 7,000 células por pozo.

MV-4-11: 25,000 células por pozo.

En el día 2, el compuesto a una concentración máxima de 5 mM se diluye de manera seriada 1:3 para un total de 8 puntos de titulación con DMSO como control. Una alícuota de 1 µL de cada punto de dilución se agrega a 249 µL de medio de crecimiento y 50 µL se agrega a un pozo que contiene células, proporcionando 10 µM de compuesto para el punto de máxima concentración. Las células se incuban durante 3 días a 37 °C en 5% de CO_2.

En el día 5, el sistema ATPlite 1 step Luminescence Assay System (Perkin Elmer # 6016739) se lleva a temperatura ambiente en conjunto con los cultivos celulares. ATPlite se agrega a cada pozo como sigue:

BCR-FMS/BaF3 y BCR-KIT/BaF3: 25 µL por pozo.

M-NFS-60: 25 µL por pozo.

M-07e: 40 µL por pozo.

BAC1.2F5: 50 µL por pozo.

MV-4-11: 40 µL por pozo.

Las células se incuban a temperatura ambiente durante 10 minutos, entonces la luminiscencia se lee en un lector Safire. La luminiscencia medica se correlaciona directamente con el número de células, de tal modo que la lectura, como una función de la concentración del compuesto, se usa para determinar

el valor de la IC_{50}.

[0437] Además, un ensayo de diferenciación de osteoclastos se usa para valorar la eficacia de los inhibidores de Fms para tratar una enfermedad ósea tal como osteoartritis. En el día 0, el medio Osteoclast Medium BulletKit (Lonza catálogo # PT-8001, que contiene Medio, FBS, L-Glutamina, PenStrep, RANKL, y M-CSF) se descongela y el FBS, L-glutamina y PenStrep del equipo se agregan a 100 ml de medio Osteoclast Precursor Basal para proporcionar el medio Osteoclast Precursor Growth Medium (OPGM). Este se calienta a 37 °C. Las células precursoras de osteoclastos (Lonza catálogo # 2T-110) congeladas en un criovial se calientan a 37 °C y se transfieren a un tubo cónico de 50 ml. El criovial se enjuaga con OPGM y se agrega por goteo al tubo cónico de células con giros, entonces el volumen se ajusta a 20-30 ml con adición de OPGM. Las células se centrifugan a 200 x g durante 15 minutos a temperatura ambiente y todo excepto aproximadamente 3 ml del sobrenadante se remueve a un nuevo tubo cónico. Las células se suspenden en el sobrenadante restante y el volumen se ajusta a 10-15 ml con OPGM agregado por goteo con giros. Las células se centrifugan a 200 x g durante 15 minutos a temperatura ambiente y todo excepto aproximadamente 1 ml del sobrenadante se remueve. Las células se resuspenden en el sobrenadante restante, se cuentan, y el volumen se ajusta con una cantidad apropiada de OPGM para proporcionar aproximadamente 1 x 10^5 células/ml. Una alícuota de 0.1 ml de células se agrega a cada pozo de una placa de 96 pozos. El compuesto que se probará se prepara en DMSO para colocar en placas a una alta concentración de 2.5 mM, con 8 puntos de diluciones en serie 1:3. Una alícuota de 1 µL de cada dilución de compuesto se agrega a una placa de polipropileno de 96 pozos de fondo en v y 0.124 ml de OPGM se agregan al compuesto. Entonces 50 µL del compuesto en OPGM se agregan a las células precursoras de osteoclastos en una placa de 96 pozos (lo que proporciona la concentración más alta de prueba de 5 µM). RANKL (2 µg) del BulletKit se reconstituye en 1 ml de OPGM, entonces se agita por vórtice y se centrifuga brevemente. Una alícuota de 792 µL de RANKL se agrega a 6 ml de OPGM y 50 µL se agregan a pozos de control bajo. Entonces 76.6 µL de M-CSF (10 µg/ml) del BulletKit se agregan a los restantes 5.8 ml de solución OPGM/RANKL (4X RANKL/M-CSF/OPGM). Una alícuota de 50 µL de esto se agrega a los pozos restantes, y el resto se almacena a 4 °C para su uso posterior. La placa se incuba a 37 °C durante 6 días, entonces la solución OPGM/RANKL/M-CSF restante se calienta a 37 °C. Los restantes aproximadamente 198 µL se combinan con 6 ml de OPGM. El medio se aspira de los pozos de osteoclastos y 100 µL de RANKL/OPGM se agregan a los controles bajos. El RANKL/OPGM restante se combina con los aproximadamente 18.5 µL de M-CSF restante. El 4X RANKL/M-CSF/OPGM restante del día 0 se diluye a 1X y se combina con la solución recién preparada. Una alícuota de 0.1 ml de esto se agrega a cada pozo de osteoclastos y se incuba a 37 °C durante 1 día. El equipo Acid Phosphatase (Cayman Chemical catálogo # 10008051) se calienta a temperatura ambiente. El regulador de ensayo se diluye 5 ml con 45 ml de agua. Para cada placa, dos tabletas de sustrato se disuelven en 4.5 ml del regulador de ensayo, mezclando por vórtice para

romper la tableta. La solución de detención se diluye 12 ml con 36 ml de agua. En una campana para cultivo celular, 20 µL de cada sobrenadante de pozo de osteoclasto se transfieren a una placa de 96 pozos. Una alícuota de 30 µL de la solución de sustrato se agrega a cada pozo y se incuba a 37 °C durante 20 minutos, entonces se agregan 100 µL de solución de detención a cada pozo. La absorbancia de cada pozo se lee a 405 nM en unlector de placas Safire. La lectura de absorbancia se grafica vs. concentración para proporcionar la IC_{50} para cada compuesto.

[0438] La siguiente tabla indica la actividad inhibitoria bioquímica de Fms y Kit y la selectividad (Kit IC_{50}/FmsIC_{50}) y la selectividad y actividad inhibitoria basada en células BCR-FMS/BaF3 y BCR-KIT/BaF3 (Kit IC_{50}/FmsIC_{50}) para compuestos ejemplares de acuerdo con la invención como se indica:

Número de compuesto	Actividad bioquímica (IC_{50} µM)			BCR/BaF3 (IC_{50} µM)		
	Fms	Kit	selectividad	Fms	Kit	selectividad
P-1496	< 0.1			< 0.1	> 0.1	> 20
P-1554	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-1562	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-1622	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-1669				< 0.1	> 0.1	> 20
P-1679	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2001	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2003	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2004	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2008	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2013	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2019	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2028	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2029	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2030	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2031	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2032	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2037	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2038	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2043	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2045	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2048	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2049	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2052	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2057	< 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2061	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2062	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2063	< 0.1	< 0.1	< 20	< 0.1	> 0.1	> 20
P-2064	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2067	< 0.1	> 0.1	> 20			
P-2070	< 0.1	< 0.1	< 20	< 0.1	> 0.1	> 20
P-2071	< 0.1	> 0.1	> 20	> 0.1	> 0.1	> 20
P-2073	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2075	< 0.1	> 0.1	> 20			
P-2078	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20

P-2079	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2081	< 0.1	< 0.1	< 20	> 0.1	> 0.1	< 20
P-2082	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2088	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2097	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2103	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2118	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2131	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2139	< 0.1	> 0.1	> 20	> 0.1	> 0.1	< 20
P-2146	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2147	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2148	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2154	< 0.1	< 0.1	< 20	< 0.1	> 0.1	< 20
P-2157	> 0.1	> 0.1	< 20	< 0.1	> 0.1	> 20
P-2163	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2165	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2172	< 0.1	< 0.1	< 20	< 0.1	< 0.1	< 20
P-2176	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2193	< 0.1	> 0.1	> 20	< 0.1	> 0.1	> 20
P-2198	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20
P-2202	< 0.1	> 0.1	< 20	< 0.1	> 0.1	< 20

[0439] La siguiente tabla indica la actividad inhibitoria bioquímica de Fms y Flt-3 y la actividad inhibitoria basada en células BCR-FMS/BaF3 y MV-4-11 para compuestos ejemplares de acuerdo con la invención que son de potencia aproximadamente igual para Fms/Flt-3 como se indica:

Número de compuesto	Bioquímica (IC_{50} μM)		Basada en células (IC_{50} μM)	
	Fms	Flt-3	BCR/BaF3 (Fms)	MV-4-11 (Flt-3)
P-1644	< 0.1	< 0.1	< 0.1	
P-1646	< 0.1	< 0.1	< 0.1	
P-2003	< 0.1	< 0.1	< 0.1	> 0.1
P-2004	< 0.1	< 0.1	< 0.1	
P-2009	< 0.1	< 0.1	< 0.1	
P-2019	< 0.1	< 0.1	< 0.1	
P-2029	< 0.1	< 0.1	< 0.1	< 0.1
P-2030	< 0.1	< 0.1	< 0.1	< 0.1
P-2031	< 0.1	< 0.1	< 0.1	< 0.1
P-2032	< 0.1	< 0.1	< 0.1	< 0.1
P-2034	< 0.1	< 0.1	< 0.1	> 0.1
P-2037	< 0.1	< 0.1	< 0.1	> 0.1
P-2038	< 0.1	< 0.1	< 0.1	< 0.1
P-2044	< 0.1	> 0.1	< 0.1	< 0.1
P-2048	< 0.1	< 0.1	< 0.1	> 0.1
P-2057	< 0.1	< 0.1	< 0.1	< 0.1
P-2165	< 0.1	< 0.1	< 0.1	> 0.1

[0440] Los compuestos P-1554, P-2001, P-2003, P-2004, P-2019, P-2028, P-2029, P-2030, P-2031, P-2032, P-2037, P-2038, P-2045, P-2048, P-2049, P-2052, P-2057, P-2061, P-2063, P-2064, P-2070, P-2146, P-2147, P-2157, P-2165, P-2176, y P-2193 demostraron una IC_{50} por debajo de 0.1 μM en el ensayo de diferenciación de osteoclastos.

[0441] Como una indicación de la solubilidad relativa, se valoró la turbidez de los compuestos en soluciones acuosas. Para valorar posibles propiedades del compuesto en diferentes compartimientos fisiológicos, tal como estómago, intestino y sangre, se usó una serie de reguladores acuosos con pH variable. De esta manera, cada compuesto se diluye en cuatro diferentes reguladores fisiológicamente relevantes y la turbidez de la solución se mide por espectrofotometría. La concentración de compuesto que demuestra turbidez al formar suficiente suspensión insoluble para elevar la densidad óptica promedio por arriba de 0.01 en tres longitudes de onda (490, 535, y 650 nm), se usa para definir el límite de solubilidad del compuesto en ese regulador.

[0442] Los compuestos se disuelven a una concentración de 25 mM en dimetilsulfóxido, entonces se diluyen en serie 1:1 en una placa de 96 pozos, diluyendo 10 veces en dimetilsulfóxido puro, con el pozo final de cada hilera siendo un dimetilsulfóxido solo. En una placa de ensayo, 99 μL de regulador apropiado se agregan a cada pozo, y 1 μL de cada dilución de muestra se agrega al regulador, alcanzando una diversidad de concentraciones totales finales en soluciones acuosas que tienen diferente pH. Los reguladores usados son Fluido Gástrico Simulado (SGF-pH 1.5) 0.5M NaCl, pH 1.5; Fluido Intestinal Simulado (SIF-pH 4.5 y pH 6.8) 0.05M NaH_2PO_4, pH 4.5 y 6.8; y Regulador Hepes (HEPES-pH 7.4) 10 mM HEPES, 150 mM NaCl, pH 7.4. Los compuestos control pireno, estriol y propranolol HCl también se valoran. Las placas se centrifugaron y entonces se mezclaron durante 1 minuto, y la absorbancia se leyó usando un Tecan Safire II para leer longitudes de onda en el intervalo visible (490, 535, y 650 nm) en cuatro ubicaciones por pozo, reflejando el grado de turbidez presente. La densidad óptica promedio para cada longitud de onda en cada pozo se graficó vs. concentración de compuesto, y la concentración en la que la curva cruza un umbral O.D. de 0.01 para cada longitud de onda se reportó como el resultado del ensayo de turbidez de punto final. El promedio de las tres longitudes de onda se usa para comparar turbidez de compuestos. Se considera que los compuestos tienen baja solubilidad si la concentración umbral es <31.3 μM, solubilidad moderada si la concentración umbral es 31.3 μM a 250 μM, y alta solubilidad si la concentración umbral es >250 μM.

[0443] La siguiente tabla indica la solubilidad relativa (L = baja, M = moderada, H = alta) con base en la concentración del umbral de turbidez a cada pH para compuestos ejemplares de acuerdo con la invención como se indica:

Número de compuesto	**umbral de turbidez** (L, M, H)			
	1.4	4.5	6.8	7.4

P-1554	H	H	M	M
P-1562	H	H	M	M
P-1622	H	M	M	M
P-1669	M	M	M	M
P-1679	M	L	L	L
P-2001	M	L	L	L
P-2003	H	M	L	L
P-2004	H	M	M	M
P-2019	H	M	M	L
P-2028	H	M	M	M
P-2029	H	M	M	M
P-2030	H	M	M	L
P-2031	M	L	L	L
P-2032	M	L	L	L
P-2037	M	L	L	L
P-2038	H	L	L	L
P-2043	H	M	M	M
P-2045	H	M	M	M
P-2048	M	L	L	L
P-2049	M	L	L	L
P-2052	H	L	L	L
P-2057	H	L	L	M
P-2061	H	M	M	L
P-2062	H	L	L	L
P-2064	H	M	L	L
P-2067	H	H	H	H
P-2071	M	L	L	L
P-2073	H	M	M	M
P-2075	H	M	L	M
P-2146	H	M	M	L
P-2165	L	L	L	L
P-2172	H	L	L	L
P-2193		L		
P-2198	M	L	L	L

[0444] **Las enzimas** CYP (Citocromo P450) son las principales enzimas del metabolismo de fármacos presentes en el hígado. La inhibición de la actividad enzimática CYP (IC_{50}) para cada uno de CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4(BFC) y CYP3A4(BQ) se determina para los compuestos, donde la inhibición del metabolismo de un sustrato conocido conduce a una disminución en la fluorescencia del producto metabolizado. La fluorescencia del producto se monitorea como una función de la concentración del compuesto.

[0445] Los compuestos se disuelven en DMSO a una concentración de 100 mM. Estos se diluyen 1 µL en 82 µL de acetonitrilo. Una alícuota de 11 µL de esta solución entonces se agrega a 204 µL de mezcla de cofactores (1.3% de sistema de Regeneración de NADPH Solución A, 1.04% de sistema de Regeneración de NADPH Solución B de BD Biosciences, 5% de acetonitrilo y 0.05% de DMSO). Estos entonces se diluyen de manera seriada 1:1 (160 µl a 160 µl de mezcla de cofactores) para un

total de 10 puntos. Una alícuota de 10 µL de esta mezcla final se distribuye en placas de ensayo de 384 pozos y se incuba durante 10 minutos a 37 °C. Enzima y mezcla de sustratos (10 µL; 0.5 pmol CYP1A2/5 µM CEC; 1.0 pmol CYP2C9/75 µM MFC; 0.5 pmol CYP2C19/25 µM CEC; 1.5 pmol CYP2D6/1.5 µM AMMC; 1.0 pmol CYP3A4/50 µM BFC; o 1.0 pmol CYP3A4/40 µM BQ) se agrega a estas placas de ensayo. Las placas de ensayo se incuban a 37 °C (CYP1A2-15 min; CYP2C9-45 min; CYP2C19, 2D6 y 3A4-30 min) y se leen en un lector de placas Tecan Safire 2 (CYP1A2, 2C19 y 3A4 409 ex/460 em; CYP2C9 y 2D6 409 ex/530 em). La señal versus concentración de compuesto se usa para determinar la IC_{50}. Las enzimas y sustratos para este ensayo se obtienen de BD Biosciences. Aunque otros factores se implican en determinar los efectos de CYP in vivo, los compuestos preferentemente tienen valores de IC_{50} de >5 µM, más preferentemente valore de IC_{50} de > 10 µM.

[0446] La siguiente tabla indica la inhibición de Cyp para compuestos ejemplares de acuerdo con la invención como se indica:

Número de compuesto	Cyp IC_{50} (µM)					
	1A2	2C19	2C9	2D6	3A4(BFC)	3A4(BFC)
P-1562	> 10	> 10	< 5	> 10	5-10	5-10
P-1622	> 10	< 5	5-10	> 10	5-10	5-10
P-1669	> 10	> 10	< 5	> 10	5-10	
P-1679	> 10	< 5	< 5	> 10	> 10	
P-2001	> 10	< 5	5-10	> 10	5-10	5-10
P-2003	> 10	5-10	< 5	> 10	5-10	> 10
P-2004	> 10	5-10	< 5	5-10	< 5	5-10
P-2019	> 10	5-10	< 5	< 5	< 5	> 10
P-2028	> 10	> 10	< 5	> 10	< 5	< 5
P-2029	> 10	< 5	< 5	> 10	5-10	5-10
P-2030	> 10	< 5	< 5	> 10	5-10	> 10
P-2031	> 10	< 5	< 5	> 10	5-10	5-10
P-2032	5-10	< 5	< 5	> 10	> 10	> 10
P-2037	> 10	< 5	< 5	> 10	5-10	> 10
P-2038	> 10	> 10	5-10	> 10	> 10	> 10
P-2043	> 10	> 10	5-10	> 10	> 10	5-10
P-2045	> 10	5-10	> 10	> 10	5-10	> 10
P-2048	> 10	> 10	> 10	> 10	> 10	> 10
P-2049	> 10	5-10	5-10	> 10	5-10	> 10
P-2052	> 10	> 10	5-10	> 10	5-10	5-10
P-2057	> 10	5-10	5-10	> 10	> 10	> 10
P-2061	> 10	> 10	5-10	> 10	> 10	5-10
P-2062	> 10	< 5	< 5	> 10	5-10	5-10
P-2063	> 10	5-10	> 10	> 10	5-10	5-10
P-2064	> 10	> 10	5-10	> 10	> 10	> 10
P-2067	> 10	< 5	< 5	> 10	< 5	> 10
P-2071	> 10	> 10	5-10	> 10	5-10	5-10
P-2073	> 10	> 10	< 5	> 10	5-10	> 10
P-2075	5-10	< 5	< 5	> 10	< 5	5-10
P-2078	> 10	> 10	< 5	> 10	< 5	> 10
P-2079	> 10	5-10	5-10	> 10	< 5	5-10

P-2081	> 10	< 5	< 5	> 10	< 5	5-10
P-2082	> 10	< 5	< 5	> 10	< 5	< 5
P-2088	> 10	< 5	< 5	> 10	5-10	5-10
P-2097	> 10	< 5	< 5	> 10	5-10	5-10
P-2103	> 10	< 5	< 5	> 10	5-10	5-10
P-2118	> 10	< 5	5-10	> 10	5-10	> 10
P-2131	> 10	5-10	< 5	> 10	< 5	> 10
P-2139	> 10	> 10	5-10	> 10	5-10	> 10
P-2146	> 10	< 5	5-10	> 10	> 10	> 10
P-2147	> 10	< 5	> 10	> 10	5-10	5-10
P-2157	> 10	> 10	> 10	> 10	5-10	> 10
P-2165	> 10	> 10	> 10	> 10	> 10	> 10
P-2172	> 10	< 5	5-10	> 10	> 10	
P-2193	> 10	> 10	> 10	> 10	> 10	> 10
P-2198	> 10	< 5	5-10	> 10	< 5	

[0447] Las propiedades farmacocinéticas de los compuestos (incluyendo cualquier forma sólida o formulaciones de los mismos) se valoran en ratas Sprague Dawley machos o perros Beagle machos. Las ratas se dosificaron diariamente con un compuesto por inyecciones IV mediante catéteres yugulares implantados quirúrgicamente o por alimentación oral (PO). Cada compuesto se preparó como una solución de reserva de 20 mg/ml en dimetilsulfóxido, que además se diluyó para proporcionar la reserva de dosificación a la concentración deseada para las formulaciones IV o PO. Para dosificación IV, la reserva de dosificación se diluyó en una mezcla 1:1:8 de Solutol ®:etanol:agua. Para dosificación PO, la reserva de dosificación se diluyó en 1% de metilcelulosa. En un formato de casete (o cada compuesto, forma sólida del mismo o formulación del mismo se hace individualmente), los compuestos se diluyen a 0.5 mg/ml cada uno para dosificación IV y 0.4 mg/ml cada uno para dosificación PO y se dosificaron a 1 mg/kg (2 ml/kg) o 2 mg/kg (5 ml/kg), respectivamente. Para animales dosificados IV, se recolectaron muestras de sangre de vena caudal con anticoagulante de heparina de litio a 5, 15, 30, y 60 minutos y 4, 8, y 24 horas post dosificación cada día. Para animales dosificados PO, se recolectaron muestras de sangre de vena caudal con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas post dosificación cada día. Los perros se dosifican diariamente por cápsulas orales en una formulación adecuada a 50 mg/ml. Se recolectaron muestras de sangre de vena cefálica con anticoagulante de heparina de litio a 30 minutos, 1, 2, 4, 8 y 24 horas post dosificación cada día. Todas las muestras se procesaron a plasma y se congelaron para análisis posterior de cada compuesto por LC/MS/MS. Los niveles plasmáticos como función de tiempo se graficaron para valorar el AUC (ng*hr/ml). Los compuestos de acuerdo con la presente invención preferentemente muestran propiedades farmacocinéticas mejoradas en relación con compuestos previamente descritos, es decir, tienen valores sustancialmente superiores para uno o más de AUC, Cmax y vida media en relación con los compuestos previamente descritos.

[0448] Un análisis de penetración del compuesto en el cerebro puede valorarse de manera similar. Cada compuesto se prepara como una solución de reserva de 100 mg/ml en sulfóxido de dimetilo, así como los compuestos control atenolol a 100 mg/ml y antipirina a 50 mg/ml. En formato de casete, hasta tres compuestos de prueba, en conjunto con atenolol y antipirina, se combinan, 180 µL cada uno, y se agregan a 17.1 ml de 1% de metilcelulosa. Los compuestos están en una suspensión que se administra en una sola dosis (10 ml por kg de peso corporal) a 2 grupos de ratas CD (8-9 semanas, n=3 por grupo) por sonda gastroesofágica, un grupo adicional de ratas se dosificó con vehículo solamente. Un grupo de ratas tratadas con el compuesto se sacrifica a las 2 horas después de la dosificación, el otro grupo a las 6 horas. Se recolecta plasma en Li-heparina y los cerebros se recolectan, se cortan en los hemisferios derecho e izquierdo, se pesan y congelan instantáneamente. Las muestras de homogenizado de cerebros (30%) y plasma se valoran por diálisis de equilibrio usando un aparato de 96 pozos de diálisis de equilibrio con una membrana de separación de 5K MW (The Nest Group, Inc.) conforme al protocolo del vendedor con las muestras en un lado de la membrana de diálisis y un volumen igual de 1XPBS en el otro lado. El aparato se incuba durante la noche a 37 °C en un rotador de placas (The Nest Group, Inc.). Las concentraciones de los compuestos en ambos lados se analizan por LC/MS/MS para calcular la recuperación del balance de masa. La concentración en el lado del PBS se calcula usando una curva estándar generada para cada compuesto. La concentración de PBS es la concentración del compuesto libre, mientras el lado con la muestra biológica proporciona la concentración en el plasma o cerebro.

[0449] Atributos adicionales del complejo pueden usarse para demostrar las propiedades mejoradas, tales como comparación de la tasa de disolución intrínseca de un complejo de citrato sustancialmente amorfo preparado de manera similar o formulación del mismo as en comparación con aquel de una forma cristalina del compuesto o formulación similar del mismo en fluido gástrico simulado (SGF) sin enzima y en fluido intestinal simulado (SIF). Una gránulo de la muestra de prueba se disuelve en el fluido apropiado, y la absorbancia de luz UV como una función del tiempo se mide a 254 nm (SGF) o 310 nm (SIF) y se grafica.

Ejemplo 28: Sistema de prueba de modelos *In vivo*

[0450] Para pruebas *in vivo*, un sistema de modelo animal adecuado puede seleccionarse para su uso. Por ejemplo, para esclerosis múltiple, el sistema de encefalomielitis alérgica experimental en roedores (EAE) se usa comúnmente. Este sistema se describe, por ejemplo, en Steinman, 1996, Cell 85:299-302 y Secor et al., 2000, J Exp. Med 5:813-821, los cuales se incorporan en este documento para referencia en su totalidad. Para artritis reumatoide (RA), el modelo en animales pequeños de artritis inducida por colágena tipo II (CIA) de artritis reumatoide (RA) puede usarse para la prueba. Este modelo se describe, por ejemplo, en Wooley, et al. Current Rheumatology Reviews, 2008, 4 : 277–287, que se incorpora en este documento para referencia en su totalidad.

[0451] De manera similar, otros sistemas de modelos pueden usarse para evaluar los compuestos descritos en este documento. Numerosos compuestos descritos en este documento, incluyendo los compuestos de las Fórmulas I, I', II, II', IIa, III, y III' (por ejemplo, P-1496, P-1622, P-1669, P-1679, P-2001, P-2028, P-2029, P-2030, P-2038, P-2043, P-2045, P-2048, P-2049, P-2052, P-2057, P-2061, P-2062, P-2063, P-2064, P-2067, P-2070, P-2071, P-2073, P-2075, P-2078, P-2088, P-2097, P-2103, P-2118, P-2139, P-2157, P-2165, P-2176, P-2193, P-1554, P-1562, P-2003, P-2004, P-2008, P-2013, P-2019, P-2031, P-2032, P-2037, P-2079, P-2081, P-2082, P-2131, P-2146, P-2147, P-2148, P-2154, P-2163, P-2172, P-2198, P-2202, P-1644, P-1646, P-1667, P-2003, P-2004, P-2009, P-2019, P-2029, P-2030, P-2031, P-2032, P-2034, P-2037, P-2038, P-2040, P-2041, P-2044, P-2047, P-2048, P-2050, P-2057 y P-2065; los compuestos dados a conocer en los párrafos [0038], [0079], [0094], [0102], [0103], y [0104]; y los compuestos descritos en los Ejemplos), o composiciones de los mismos, hidratos o solvatos de los mismos, se prueban en ratones para el tratamiento de diversas enfermedades y padecimientos como se describe en este documento.

Modelo en ratones de artritis reumatoide inducida por colagenasa (RA).

Métodos: Inyectiones intradérmicas con colágena-CFA, seguidas por un refuerzo de colágena por inyección intraperitoneal (ip) en el día 21 induce artritis reumatoide en una diversidad de cepas de ratones, especialmente el genotipo DBA/1 usado en este etudio (Brand et al., 2004; Wooley et al., 1981). La enfermedad se cuantifica y registra por conteos clínicas usando una escala de of 0–4 por pata. El conteo registra el grado y magnitud de la hinchazón y rubor en cada dedo y articulación y culmina en ausencia del uso de las patas individuales frontal o posterior. Los conteos se acumulan por animal lo que resulta en un conteo máximo de 16, lo que indica que los animales evitan el uso de todas las patas. Los grupos se equilibraron para conteo de enfermedad en el día 21 después de la inmunización inicial cuando el conteo clínico promedio fue de 2.5 para todos los animales. El tratamiento fue durante 21 días con dosificación oral diaria con los siguientes grupos de dosificación: vehículo, y 10 mg/kg, 20 mg/kg y 50 mg/kg de los compuestos de la invención.

Resultados

[0452] La administración oral de los compuestos de la invención inhibió el desarrollo clínico de la enfermedad en el modelo murino CIA en una forma dependiente de la dosis con respuestas significativas en todas las dosis probadas (10, 20 y 50 mg/kg qd). El análisis histopatológico de las articulaciones mostró inhibición de la inflamación, resorción ósea, daño de cartílagos y formación de cataratas por el tratamiento con los compuestos de la invención. El mecanismo de acción de los compuestos de la invención se confirmó por los conteos reducidos para macrófagos y osteoclastos en las articulaciones.

[0453] La administración oral diaria de los inhibidores de cinasa Fms descritos en este documento mostró, en todos los niveles de dosis probados (10, 20 y 50 mg/kg) un rápido beneficio as en comparación con el vehículo control, como se evidencia por los conteos clínicos reducidos, que reflejan menos hinchazón y rubor de las extremidades. Este beneficio clínico se confirmó por conteos histopatológicos reducidos para inflamación, daño al cartílago, formación de cataratas y destrucción ósea. Los conteos para macrófagos y osteoclastos se redujeron en los tejidos de las articulaciones, lo que confirma que el modo de acción de los compuestos descritos en este documento es al inhibir la tirosina cinasa del receptor de Fms, el cual es crucial para la proliferación y diferenciación de estos linajes celulares. Las concentraciones plasmáticas de los grupos dosificados se extrajeron a las 2 h después de que la dosificación mostró una clara respuesta proporcional a la dosis.

[0454] Todas las patentes y otras referencias citadas en la especificación son indicativas del nivel de habilidad de los expertos en la técnica a la cual pertenece la invención, y se incorporan para referencia en sus totalidades, incluyendo cualesquier tablas y figuras, en la misma magnitud como si cada referencia se hubiera incorporado para referencia en su totalidad individualmente.

[0455] Un experto en la técnica puede apreciar fácilmente que la presente invención se adapta bien para obtener los fines y ventajas mencionadas, así como aquellas inherentes en ello. Los métodos, variaciones, y composiciones descritas en este documento, como actualmente representativas de las modalidades preferidas, son ejemplares y no pretenden ser limitaciones en el alcance de la invención. Los cambios en ello y otros usos que se les ocurrirán a los expertos en la técnica, que se abarcan dentro del espíritu de la invención, se definen por el alcance de las reivindicaciones.

[0456] La invención ilustrativamente descrita en este documento de manera favorable puede practicarse en ausencia de cualquier elemento o elementos, limitación o limitaciones que no se describen específicamente en este documento. De esta manera, por ejemplo, en cada caso en este documento cualquiera de los términos "que comprende", "que consiste esencialmente de" y "que consiste de" puede reemplazarse con cualquiera de los otros dos términos. De esta manera, para una modalidad de la invención usando uno de los términos, la invención también incluye otra modalidad en donde uno de estos términos se reemplaza con otro de estos términos. En cada modalidad, los términos tienen su significado establecido. De esta manera, por ejemplo, una modalidad puede abarcar un método "que comprende" una serie de etapas, otra modalidad puede abarcar un método "que consiste esencialmente de" las mismas etapas, y una tercera modalidad puede abarcar un método "que consiste de" las mismas etapas. Los términos y expresiones que se han empleado se usan como términos de descripción y no de limitación, y no hay intención que en el uso de tales términos y expresiones se excluya cualesquier equivalentes de los atributos mostrados y descritos o porciones de los mismos, pero se reconoce que diversas modificaciones son posibles dentro del alcance de la invención reclamada. De esta manera, debe entenderse que, aunque la presente invención se ha

descrito específicamente por modalidades preferidas y atributos opcionales, la modificación y variación de los conceptos descritos en este documento puede reordenarse por los expertos en la técnica, y que tales modificaciones y variaciones se consideran dentro del alcance de esta invención como se define por las reivindicaciones adjuntas.

[0457] Además, donde los atributos o aspectos de la invención se describan en cuanto a grupos de Markush u otra agrupación de alternativas, los expertos en la técnica reconocerán que la invención también se describe en consecuencia en cuanto a cualquier miembro individual o subgrupo de miembros del grupo de Markush u otro grupo.

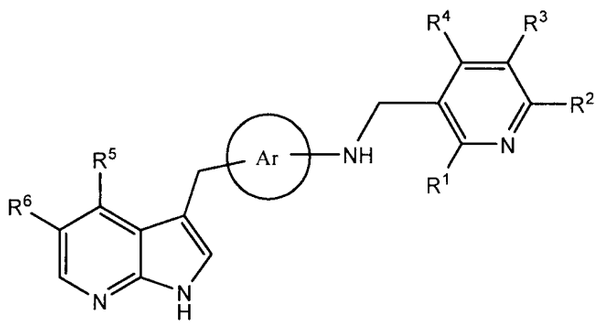
[0458] También, a menos que se indique lo contrario, donde diversos valores numéricos se proporcionan para las modalidades, las modalidades adicionales se describen al tomar cualesquier 2 valores diferentes como los puntos finales de un intervalo. Tales intervalos están también dentro del alcance de la invención descrita.

[0459] De esta manera, las modalidades adicionales están dentro del alcance de la invención y dentro de las siguientes reivindicaciones.

REIVINDICACIONES

Lo que se reclama es:

1. Un compuesto que tiene la estructura química de la Fórmula I',

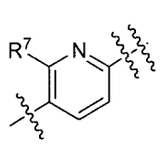
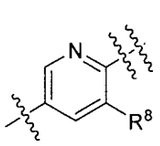
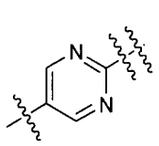
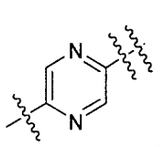
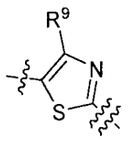


Fórmula I'

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

Ar se selecciona del grupo que consiste de:

 ,  ,  ,  , y  ; en donde indica el punto de unión de Ar a $-CH_2-$ de la Fórmula I y en donde  indica el punto de unión de Ar a -NH- de la Fórmula I;

R^1, R^2, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, halógeno, alquilo inferior, alquilo inferior sustituido con halógeno, alcoxi inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, y $-N(H)-S(O)_2-R^{43}$, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean –H y uno de R^1, R^2, R^3 y R^4 sea diferente a hidrógeno, en donde:

R^{40} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{41}, R^{42} y R^{43} son alquilo inferior;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es H, halógeno o alquilo inferior;

R^8 es H, halógeno o alcoxi inferior;

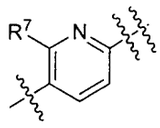
R^9 es H o halógeno;

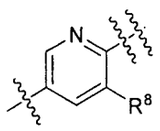
R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con -O-CH_3, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

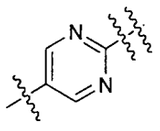
R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

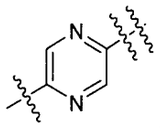
R^{12} y R^{15} son cada uno independientemente alquilo inferior,

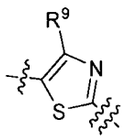
con la condición de que el compuesto sea diferente a aquel establecido en la Tabla 1.

2. El compuesto de conformidad con la reivindicación 1, en donde Ar es  .

3. El compuesto de conformidad con la reivindicación 1, en donde Ar es  .

4. El compuesto de conformidad con la reivindicación 1, en donde Ar es  .

5. El compuesto de conformidad con la reivindicación 1, en donde Ar es  .

6. El compuesto de conformidad con la reivindicación 1, en donde Ar es  .

7. El compuesto de conformidad con cualquiera de las reivindicaciones 1-6, en donde:

i) R^1, R^3 y R^4 son H y R^2 es halógeno; o

ii) R^1, R^2 y R^3 son –H, y R^4 es alquilo inferior halo sustituido; o

iii) R^1 y R^4 son –H y R^2 es alcoxi inferior; o

iv) R^3 es halógeno; o

v) R^2 y R^4 son -H, R^1 es alcoxi inferior y R^3 es halógeno.

8. El compuesto de conformidad con la Reivindicación 7, en donde:

i) R^1, R^2 and R^3 son -H y R^4 es CF_3; o

ii) R^1 y R^4 son –H y R^2 es $–OCH_3$; o

iii) R^3 es F; o

iv) R^2 y R^4 son -H, R^1 es OCH_3 y R^3 es F.

9. El compuesto de conformidad con cualquiera de las reivindicaciones 1-8, en donde R^5 es -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo

10. El compuesto de conformidad con cualquiera de las reivindicaciones 1-8, en donde R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, y $-N(H)-S(O)_2-R^{15}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo.

11. El compuesto de conformidad con la reivindicación 10, en donde R^6 es halo, alquilo inferior o alquilo inferior sustituido con flúor.

12. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 y 7-9, en donde R^7 es H, halógeno o alquilo inferior.

13. El compuesto de conformidad con la reivindicación 12, en donde, R^7 es H, -F, -Cl, Br o $–CH_3$.

14. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 3 y 7-9, en donde R^8 es H, halógeno o alcoxi inferior.

15. El compuesto de conformidad con la reivindicación 14, en donde, R^8 es H, -F, -Cl, Br o $–OCH_3$.

16. El compuesto de conformidad con la reivindicación 1, 4 y 7-9, en donde R^9 es H o halógeno.

17. El compuesto de conformidad con la reivindicación 16, en donde R^9 es -H o -Cl

18. El compuesto de conformidad con la Reivindicación 1, en donde:

R^1, R^3 y R^4 son -H y R^2 es -F, -Cl o -Br; o R^1, R^2 y R^3 son -H y R^4 es $-CF_3$; o R^1 y R^4 son -H, R^2 es $-O-CH_3$, y R^3 es -F; o R^2 y R^4 son -H, R^1 es $-O-CH_3$, y R^3 es -F;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, y $-N(H)-S(O)_2-R^{15}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es -H, -F, -Cl, o $-CH_3$;

R^8 es -H, -F, $-CH_3$, o $-O-CH_3$;

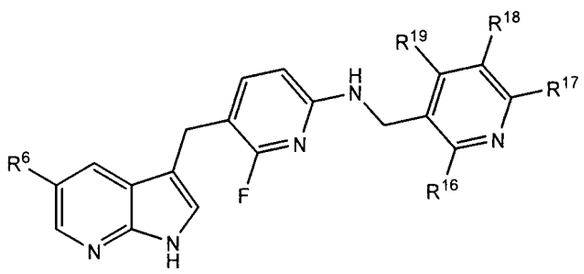
R^9 es -H o -Cl;

R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con $-O-CH_3$, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

R^{12} y R^{15} son cada uno independientemente alquilo inferior.

19. El compuesto de conformidad con la reivindicación 1, que tiene la Fórmula II':



Fórmula II'

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente del grupo que consiste de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, alquilo inferior

sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}, siempre y cuando al menos dos de R^{16}, R^{17}, R^{18} y R^{19} sean -H;

R^{20} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{21} es alquilo inferior;

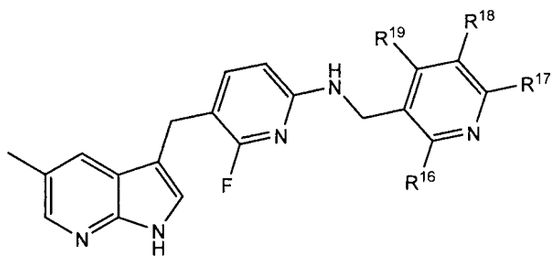
R^{22} es alquilo inferior; y

R^{23} es alquilo inferior.

20. El compuesto de conformidad con la reivindicación 19, en donde R^6 se selecciona del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo.

21. El compuesto de conformidad con la reivindicación 20, en donde R^6 es F, Cl, Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} o -N(H)-$S(O)_2$-R^{15}.

22. El compuesto de conformidad con la reivindicación 19, que tiene la Fórmula II:

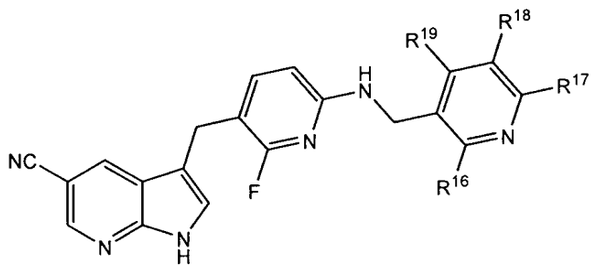


Fórmula II.

23. El compuesto de conformidad con cualquiera de las reivindicaciones 19-22, en donde R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor , alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -$N(R^{22})_2$, y -N(H)-$S(O)_2$-R^{23}.

24. El compuesto de conformidad con la reivindicación 23, en donde R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi.

25. El compuesto de conformidad con la reivindicación 19, que tiene la Fórmula IIa:

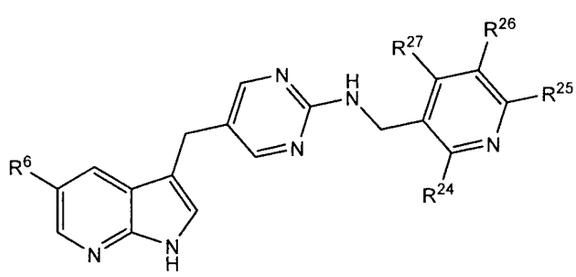


Fórmula IIa.

26. El compuesto de conformidad con la reivindicación 25, en donde R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor , alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -S(O)$_2$-R^{21}, -S(O)$_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, y -N(H)-S(O)$_2$-R^{23}.

27. El compuesto de conformidad con la reivindicación 26, en donde R^{16}, R^{17}, R^{18} y R^{19} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi.

28. El compuesto de conformidad con la reivindicación 1, que tiene la Fórmula III':



Fórmula III'

o una sal, un profármaco, un tautómero o un estereoisómero de los mismos,

en donde:

R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente del grupo que consiste de -H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, alcoxi inferior, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, -O-R^{28}, -S(O)$_2$-R^{29}, -S(O)$_2$-N(H)-R^{30}, -N(H)-R^{30}, -N(R^{30})$_2$, y -N(H)-S(O)$_2$-R^{31}, siempre y cuando al menos dos de R^{24}, R^{25}, R^{26} y R^{27} sean -H;

R^{28} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{29} es alquilo inferior;

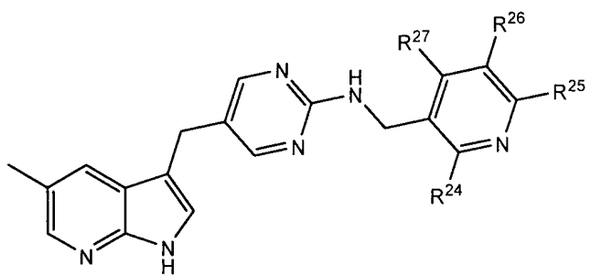
R^{30} es alquilo inferior; y

R^{31} es alquilo inferior.

29. El compuesto de conformidad con la reivindicación 28, en donde R^6 se selecciona del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, -O-R^{13}, -C(O)-N(H)-R^{14}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14}, -N(H)-C(O)-R^{15}, y -N(H)-$S(O)_2$-R^{15}, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo.

30. El compuesto de conformidad con la reivindicación 29, en donde R^6 es F, Cl, Br, alquilo inferior, alquilo inferior sustituido con flúor, alquenilo inferior, -CN, -C(O)-N(H)-R^{14}, -N(H)-C(O)-R^{15}, -C(O)-O-R^{14}, -$S(O)_2$-R^{15}, -$S(O)_2$-N(H)-R^{14} o -N(H)-$S(O)_2$-R^{15}.

31. El compuesto de conformidad con la reivindicación 28, que tiene la Fórmula III:



Fórmula III.

32. El compuesto de conformidad con cualquiera de las reivindicaciones 28-31, en donde R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo inferior sustituido con flúor , alcoxi inferior, alquilo inferior sustituido con metoxi, cicloalquilamino, -CN, -O-R^{20}, -$S(O)_2$-R^{21}, -$S(O)_2$-N(H)-R^{22}, -N(H)-R^{22}, -N(R^{22})$_2$, y -N(H)-$S(O)_2$-R^{23}.

33. El compuesto de conformidad con la reivindicación 32, en donde R^{24}, R^{25}, R^{26} y R^{27} se seleccionan cada uno independientemente de H, halógeno, alquilo inferior, alcoxi inferior, alquilo inferior halo sustituido, -OR^{20}, o alquilo inferior sustituido con alcoxi.

34. Un compuesto seleccionado del grupo que consiste de:

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-dimetoxi-piridin-3-ilmetil)-amina (**P-1496**),

[6-Fluoro-5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1622**),

N-(3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-acetamida (**P-1669**),

N-(3-{6-[(6-Cloro-piridin-3-ilmetil)-amino]-2-fluoro-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-il)-metanosulfonamida (**P-1679**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2001**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2028**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2043**),

[6-Fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2045**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2049**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-2052**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

(5-Fluoro-2-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2061**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2062**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2063**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-metoxi-piridin-3-ilmetil)-amina (**P-2064**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2067**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-trifluorometil-piridin-3-ilmetil)-amina (**P-2070**),

(5-Fluoro-2-metoxi-piridin-4-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2071**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2073**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(2-metil-piridin-4-ilmetil)-amina (**P-2075**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2078**),

(6-Cloro-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2088**),

(2,6-Dimetoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2097**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-3-ilmetil)-amina (**P-2103**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-piridin-4-ilmetil)-amina (**P-2118**),

(2-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2139**),

3-{[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-ilamino]-metil}-5-fluoro-1-metil-1H-piridin-2-ona (**P-2157**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-2176**),

3-{2-Fluoro-6-[(5-fluoro-2-metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridin-5-carbonitrilo (**P-2193**),
5-[(5-bromo-1H-pirrolo[2,3-b]piridin-3-il)metil]-6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]piridin-2-amina **(P-2203),**
3-[[2-fluoro-6-[(5-fluoro-6-metoxi-3-piridil)metilamino]-3-piridil]metil]-1H-pirrolo[2,3-b]piridin-5-carbonitrilo **(P-2204),**
6-cloro-N-[(5-fluoro-2-metoxi-3-piridil)metil]-5-[(5-metil-1H-pirrolo[2,3-b]piridin-3-il)metil]piridin-2-amina **(P-2205),**
6-fluoro-N-[(5-fluoro-6-metoxi-3-piridil)metil]-5-[[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-3-il]metil]piridin-2-amina **(P-2206)** y
una sal, profármaco, tautómero, o estereoisómero de los mismos.

35. Un compuesto seleccionado del grupo que consiste de:

(6-Metoxi-piridin-3-ilmetil)-[3-metil-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1554**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-1562**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2003**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina (**P-2004**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3,4-difluoro-bencil)-amina (**P-2008**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-metil-bencil)-amina (**P-2013**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

(6-Metil-piridin-2-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2079**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina (**P-2081**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-pirrolidin-1-il-piridin-2-ilmetil)-amina (**P-2082**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-metil-piridin-2-ilmetil)-amina (**P-2131**),

[3-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2146**),

[3-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2147**),

(2-Ciclopentiloxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2148**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2154**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina (**P-2163**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2172**),

(2-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2198**),

(3-fluoro-5-{[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido etanosulfónico (**P-2202**), y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

36. Un compuesto seleccionado del grupo que consiste de:

(6-Trifluorometil-piridin-3-ilmetil)-[5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1644**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-trifluorometil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-1646**),

[5-(5-Ciclopropil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-1667**),

(6-Cloro-piridin-3-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2003**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-fluoro-piridin-3-ilmetil)-amina (**P-2004**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-fluoro-5-trifluorometil-bencil)-amina (**P-2009**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2019**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2029**),

[6-Fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2030**),

[6-Fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-2031**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2032**),

(2-Cloro-bencil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2034**),

(4-Cloro-bencil)-[6-fluoro-5-(4-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2037**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-2038**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2040**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2041**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2044**),

(5-Cloro-piridin-2-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2047**),

(5-Fluoro-6-metoxi-piridin-3-ilmetil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2048**),

(4-Cloro-bencil)-[6-fluoro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-2050**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-2057**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(5-fluoro-6-metoxi-piridin-3-ilmetil)-amina (**P-2165**), y

cualquier sal, profármaco, tautómero, o estereoisómero de los mismos.

37. Una composición que comprende un compuesto de cualquiera de las reivindicaciones **1-36** y un excipiente o portador farmacéuticamente aceptable.

38. Un equipo que comprende un compuesto de cualquiera de las reivindicaciones 1-36 o una composición de la reivindicación 37.

39. Un compuesto de cualquiera de las reivindicaciones 1-36 para su uso como medicamento.

40. Un método para tratar un sujeto que adolece o está en riesgo de enfermedad o padecimiento, el método comprende administrar al sujeto en necesidad de ello una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones **1-36**, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, enfermedad de Parkinson, artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular , nefropatía diabética, e hipertrofia renal, cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal y leucemia mieloide aguda.

41. El método de conformidad con la reivindicación 40, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, enfermedad de Parkinson, artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular , nefropatía diabética, e hipertrofia renal.

42. El método de conformidad con la reivindicación 40, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide, y esclerosis múltiple.

43. El método de conformidad con la reivindicación 40, en donde la enfermedad o padecimiento es leucemia mieloide aguda.

44. Un método para tratar un sujeto que adolece o está en riesgo de enfermedad o padecimiento, el método comprende administrar al sujeto en necesidad de ello una cantidad efectiva de un compuesto de la reivindicación 34, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de esclerosis múltiple, glioblastoma, enfermedad de Alzheimer, enfermedad de Parkinson, artritis reumatoide, osteoartritis, aterosclerosis, lupus eritematoso sistémico, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular , nefropatía diabética, e hipertrofia renal.

45. Un método para tratar un sujeto que adolece o está en riesgo de enfermedad o padecimiento, el método comprende administrar al sujeto en necesidad de ello una cantidad efectiva de un compuesto de la reivindicación **35**, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de cáncer de mama metastásico, cáncer de próstata, mieloma múltiple, melanoma, leucemia mieloide aguda, metástasis de cerebro, neurofibromatosis, tumores de estroma gastrointestinal, artritis reumatoide, y esclerosis múltiple.

46. Un método para tratar un sujeto que adolece o está en riesgo de un enfermedad o padecimiento, el método comprende administrar al sujeto en necesidad de ello una cantidad efectiva de un compuesto de la reivindicación **36**, en donde la enfermedad o padecimiento es leucemia mieloide aguda.

47. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones **1-36** y otra fármaco, en donde el otro fármaco se selecciona de:

i) un agente alquilante seleccionado de adozelesina, altretamina, bizelesina, busulfano, carboplatina, carbocuona, carmustina, clorambucil, cisplatina, ciclofosfamida, dacarbazina, estramustina, fotemustina, hepsulfamo, ifosfamida, improsulfano, irofulveno, lomustina, mecloretha mina, melfalano, oxaliplatina, piposulfano, semustina, estreptozocina, temozolomida, tiotepa, y treosulfano;

ii) un antibiótico seleccionado de bleomicina, dactinomicina, daunorubicina, doxorubicina, epirubicina, idarubicina, menogaril, mitomicina, mitoxantrona, neocarzinostatina, pentostatina, y plicamicina; un antimetabolito, incluyendo, pero sin limitarse a, azacitidina, capecitabina, cladribina, clofarabina, citarabina, decitabina, floxuridina, fludarabina, 5-fluorouracilo, ftorafur, gemcitabina, hidroxiurea, mercaptopurina, metotrexato, nelarabina, pemetrexed, raltitrexed, tioguanina, y trimetrexato;

iii) un agente inmunoterapia seleccionado de alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, y 90 Y ibritumomab tiuxetano; una hormona o antagonista de hormonas, incluyendo, pero sin limitarse a, anastrozol, andrógenos, buserelina, dietilstilbestrol, exemestano, flutamida, fulvestrant, goserelina, idoxifeno, letrozol, leuprólido, magestrol, raloxifeno, tamoxifeno, y toremifeno;

iv) un taxano seleccionado de DJ-927, docetaxel, TPI 287, paclitaxel y DHA-paclitaxel;

v) un retinoide seleccionado de alitretinoina, bexaroteno, fenretinida, isotretinoina, and tretinoina;

vi) un alcaloide seleccionado de etopósido, homoharringtonina, tenipósido, vinblastina, vincristina, vindesina, y vinorelbina;

vii) un agente antiangiogénico seleccionado de AE-941 (GW786034, Neovastat), ABT-510, 2-metoxiestradiol, lenalidomida, y talidomida;

viii) un inhibidor de topoisomerasa seleccionado de amsacrina, edotecarina, exatecano, irinotecano (también metabolito activo SN-38 (7-etil-10-hidroxi-camptotecina)), rubitecano, topotecano, y 9-aminocamptotecina;

ix) un inhibidor de cinasas seleccionado de erlotinib, gefitinib, flavopiridol, mesilato de imatinib, lapatinib, sorafenib, malato de sunitinib, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hidroxistaurosporina), y vatalanib;

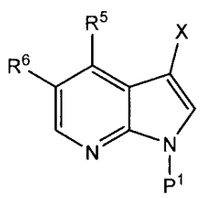
x) un inhibidor orientado de transducción de señales seleccionado de bortezomib, geldanamicina, y rapamicina;

xi) un modificador de las respuestas biológicas seleccionado de imiquimod, interferón-α, e interleucina-2; y

xii) un agente quimioterapéutico seleccionado de 3-AP (3-amino-2-carboxialdehído tiosemicarbazona), altrasentan, aminoglutetimida, anagrélido, asparaginasa, briostatina-1, cilengitida, elesclomol, mesilato de eribulina (E7389), ixabepilona, lonidamina, masoprocol, mitoguanazona, oblimerseno, sulindaco, testolactona, tiazofurina, inhibidores de mTOR (por ejemplo, temsirolimus, everolimus, deforolimus), inhibidores de PI3K (por ejemplo, BEZ235, GDC-0941, XL147, XL765), inhibidores de Cdk4 (por ejemplo, PD-332991), inhibidores de Akt, inhibidores de Hsp90 (por ejemplo, tanespimicina) e inhibidores de farnesiltransferasa (por ejemplo, tipifarnib).

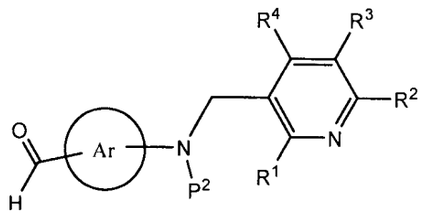
48. Un método para preparar un compuesto de la Fórmula I de acuerdo con la reivindicación 1, el método comprende:

contactar un compuesto de la Fórmula IV:



Fórmula IV

con un compuesto de la Fórmula V:



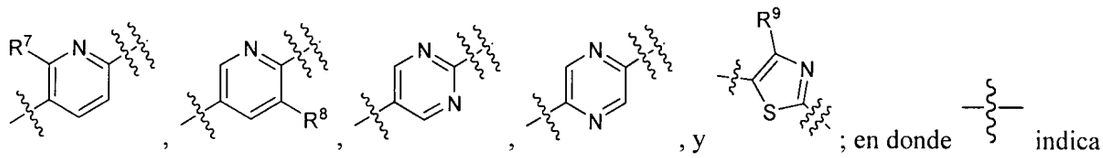
Fórmula V

bajo condiciones suficientes para formar el compuesto de la Fórmula I, en donde:

P^1 y P^2 son cada uno independientemente un grupo protector amino;

X es H o halógeno;

Ar se selecciona del grupo que consiste de:



; en donde indica el punto de unión de Ar a $-CH_2-$ de la Fórmula I y en donde  indica el punto de unión de Ar a -NH- de la Fórmula I;

R^1, R^2, R^3 y R^4 se seleccionan cada uno independientemente del grupo que consiste de –H, alquilo inferior, alquilo inferior sustituido con halógeno, alquilo inferior sustituido con alcoxi, cicloalquilamino, -CN, $-O-R^{40}$, $-S(O)_2-R^{41}$, $-S(O)_2-N(H)-R^{42}$, $-N(H)-R^{42}$, $-N(R^{42})_2$, y $-N(H)-S(O)_2-R^{43}$, siempre y cuando al menos dos de R^1, R^2, R^3 y R^4 sean –H y uno de R^1, R^2, R^3 y R^4 sea diferente a hidrógeno, en donde:

R^{40} es alquilo inferior, alquilo inferior sustituido con flúor, alquilo inferior sustituido con metoxi, o cicloalquilo;

R^{41}, R^{42} y R^{43} son alquilo inferior;

R^5 se selecciona del grupo que consiste de -H, -F, -Cl, -Br, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{10}$, $-C(O)-N(H)-R^{11}$, $-C(O)-O-R^{11}$, $-S(O)_2-R^{12}$, $-S(O)_2-N(H)-R^{11}$, $-N(H)-C(O)-R^{12}$, y $-N(H)-S(O)_2-R^{12}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^6 se selecciona del grupo que consiste de H, halógeno, alquilo inferior, alquilo sustituido con halógeno, alquenilo inferior, alquinilo inferior, cicloalquilo, fenilo, pirazolilo, -CN, $-O-R^{13}$, $-C(O)-N(H)-R^{14}$, $-C(O)-O-R^{14}$, $-S(O)_2-R^{15}$, $-S(O)_2-N(H)-R^{14}$, $-N(H)-C(O)-R^{15}$, y $-N(H)-S(O)_2-R^{15}$, en donde el pirazolilo se sustituye opcionalmente con alquilo inferior o heterocicloalquilo;

R^7 es H, halógeno o alquilo inferior;

R^8 es H, halógeno, alquilo inferior o alcoxi inferior;

R^9 es H o halógeno;

R^{10} y R^{13} son independientemente -H, alquilo inferior, alquilo inferior sustituido con $-O-CH_3$, alquilo inferior sustituido con di-alquilamina, o alquilo inferior sustituido con heterocicloalquilo;

R^{11} y R^{14} son independientemente hidrógeno o alquilo inferior; y

R^{12} y R^{15} son cada uno independientemente alquilo inferior.

49. Un uso de un compuesto de la reivindicación 34 para modular de manera selectiva la actividad de cinasa Fms.

50. Un uso de un compuesto de la reivindicación 35 para modular la actividad de cinasas Fms/Kit.

51. Un uso de un compuesto de la reivindicación 36 para modular la actividad de cinasas Fms/Flt-3.

52. Una composición que comprende un compuesto de cualquiera de las reivindicaciones 34-36 y un excipiente o portador farmacéuticamente aceptable.

RESUMEN

Se describen compuestos y sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, formas de los mismos y usos de los mismos. En ciertos aspectos y modalidades, los compuestos descritos o sales de los mismos, formulaciones de los mismos, conjugados de los mismos, derivados de los mismos, o formas de los mismos son activos sobre proteína cinasa Fms, o sobre proteína cinasa Fms y Kit, o sobre proteína cinasa Fms y Flt-3 . También se describen métodos de uso de los mismos para tratar enfermedades y padecimientos, incluyendo enfermedades y padecimientos asociado con la actividad de proteína cinasa Fms, proteína cinasa Kit, o proteína cinasa Flt-3 incluyendo artritis reumatoide, osteoartritis, esclerosis múltiple, enfermedad de Alzheimer, enfermedad de Parkinson, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, hipertrofia renal, leucemia mieloide aguda, melanoma, mieloma múltiple, cáncer de mama metastásico, cáncer de próstata, cáncer pancreático, neurofibromatosis, metástasis de cerebro, y tumores de estroma gastrointestinal.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 039363-5303	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/55519	International filing date *(day/month/year)* 04 November 2010 (04.11.2010)	(Earliest) Priority Date *(day/month/year)* 06 November 2009 (06.11.2009)
Applicant PLEXXIKON, INC.		

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

This international search report consists of a total of 7 sheets.

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

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

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

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

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

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

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

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

6. With regard to the **drawings**,

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

   ☐ as suggested by the applicant.

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

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/55519

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-17, 37-43 and 47
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/55519

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90; A61K 31/519 (2010.01)
USPC - 514/265.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/265.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/158; 514/264.1; 514/415; 514/438; 514/443-444; 514/461; 514/466 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB
Google: Scholar/patents: compounds modulating c-kit pyrrolo pyridine indole thiazole fms flt kinase inhibitors pyrimidine myeloid leukemia multiple sclerosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2009/0076046 A1 (ZHANG et al.) 19 March 2009 (19.03.2009) para [0012]-[0027], [0039], [0046], [0083], [0738], [0742], [0749], [0759]-[0760], [1049], [1056]; Schemes 15-16	1-8, 18-36, 44-46, 48-52

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 2010 (28.12.2010)	14 JAN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-073061- -00000-0000

Fecha: 2012-05-04 13:17:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 300

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

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

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

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

Completa ☐ Incompleta ☐