CSA055377
Organizacion y
Digitalizacion CSA Ltda

1/2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

1/2

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-52610

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS QUE MODULAN ACTIVIDAD C-FMS Y/O C-KIT Y USOS PARA ELLOS

SOLICITANTE: PLEXXIKON, INC.

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 21 de Mayo de 2009

P2009/000084

OLARTERAISBECK

OLARTE RAISBECK MOU

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-052610- -00000-0000
Fecha: 2009-05-21 16:49:11 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 434

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000084**

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 E.U.A
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.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/USP2007/085289 Fecha Noviembre 20,2007

Publicación Internacional No. WO 2008/064255 Fecha Mayo 29, 2008

(6) **Título (54)** **COMPUESTOS QUE MODULAN ACTIVIDAD C-FMS Y/O C-KIT Y USOS PARA ELLO**

Clasificación Internacional (51) C07D 471/04, A61K 31/437

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Noviembre 22, 2006	60/860,749

(9) **Comprobante de pago No.** 09- 36,825 **Fecha** Mayo 19 de 2009

(10) **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. 07-121.351
[ ]	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:**

2

( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

C.C. 79.782.747 Bta T.P. 74.295

LISTA DE INVENTORES

PCT/US2007/085289

1. **Chao ZHANG,**
397 Springfield Plaza,
Moraga, CA 94556
Estados Unidos
Nacionalidad: China

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

3. **Prabha N. IBRAHIM,**
3380 Lubich Drive,
Mountain View,
CA 94040
Estados Unidos
Nacionalidad: Estados Unidos

4. **Dean R. ARTIS,**
50 Arlmont Drive,
Kensington, CA 94707
Estados Unidos
Nacionalidad: Estados Unidos

5. **Ryan BREMER,**
476 Weldon Avenue, Apt. 3,
Oakland, CA 94610
Estados Unidos
Nacionalidad: Estados Unidos

6. **Guoxian WU,**
240 Ventura Avenue,
Palo Alto, CA 94306
Estados Unidos
Nacionalidad: Estados Unidos

7. **Hongyao ZHU,**
91 Bolívar Drive,
Suite A, Berkeley, CA 94710
Estados Unidos
Nacionalidad: Estados Unidos

8. **Marika NESPI,**
564 San Luis Road,
Berkeley, CA 94707
Estados Unidos
Nacionalidad: Italiana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-052610- -00000-0000

Fecha: 2009-05-21 16:49:11 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 434

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 36,825
FECHA : MAYO 19 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800122	19/05/2009	1,086,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

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

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

State of California

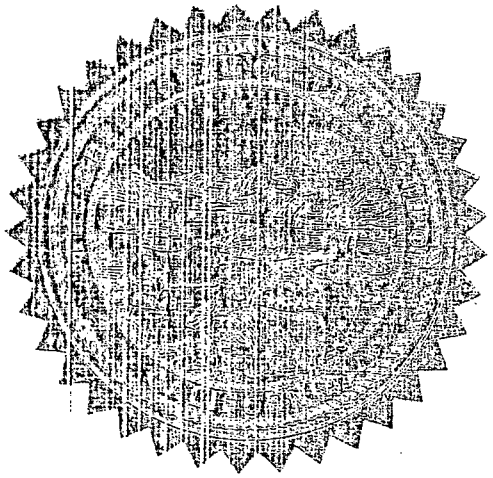
SECRETARY OF STATE
APOSTILLE

(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

BP-24 A (REV. 4-05)

OSP 05 90772

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

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

www.sdarcc.com

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

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

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

DATED: June 1, 2006 Witness by hand

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

Branch Offices Available To Serve You

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

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

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

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

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

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

Of Counsel
Guillermo Chahín
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

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

Poder

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

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

10

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

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

1. That

Dean R. Artis
of legal age and domiciled in
91 Bolivar Drive, Berkeley, California 94710 USA
signed the foregoing document.

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

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

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Dean R. Artis
mayor de edad y domiciliado
91 Bolivar Drive, Berkeley, California 94710 USA
suscribió el documento que antecede.

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

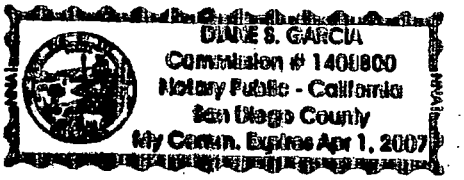
4. Que
con sede principal ubicada en

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

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

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

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



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

12

Traductor Oficial
JORGE ENRIQUE SIERRA REYES

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

Fecha: 8 de Mayo de 2006.

Firmado en constancia,

(Firmado) Gregory J. Smith, 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

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

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Traductor Oficial
JORGE E. SIERRA REYES

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.

14

Traductor Oficial
JORGE E. [illegible] REYES

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

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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

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

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

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

CERTIFIED

5. *At SAN DIEGO, California*

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

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

8. *No. 137384*

9. *Stamp/Seal*

10. *Signature*

Bruce McPherson
Secretary of State

BY Cheryl Allen

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NP-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

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

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(760) 940-6868

CERTIFICATE OF THE PRESIDENT AND SECRETARY

OF

PLEXXIKON INC.

91 Bolivar Drive
Berkeley, CA 94710

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

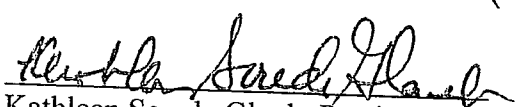
1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

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

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

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

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



Kathleen Sereda Glaub, President and Secretary

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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 GLASER (Name(s) of Signer(s))

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

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

WITNESS my hand and official seal.

Signature of Notary Public

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

OPTIONAL

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

Description of Attached Document

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

Signer(s) Other Than Named Above:

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Signer's Name:

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

Signer Is Representing: PLEXXIKON INC

RIGHT THUMBPRINT OF SIGNER
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(54) Title: COMPOUNDS MODULATING C-FMS AND/OR C-KIT ACTIVITY AND USES THEREFOR

(57) Abstract: Compounds active on the receptor protein tyrosine kinases c-kit and/or c-fms are provided herewith. Also provided herewith are compositions useful for treatment of c-kit mediated diseases or conditions and/or c-fms-mediated diseases or conditions, and methods for the use thereof.

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COMPOUNDS MODULATING C-FMS AND/OR C-KIT ACTIVITY AND USES THEREFOR

RELATED PATENT APPLICATIONS

[0001] This application claims priority to U.S. Provisional App. No. 60/860,749, entitled "Compounds Modulating c-Fms and c-Kit Activity and Uses Therefor", filed November 22, 2006, and is related to U.S. Patent App. No. 11/435,381, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed May 16, 2006, which claims the benefit of U.S. Provisional App. No. 60/682,063, entitled "Compounds Modulating c-Kit Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/682,051, entitled "Compounds Modulating c-Fms Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/682,042, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/692,750, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed June 22, 2005, and U.S. Provisional App. No. 60/692,960, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed June 22, 2005, all of which are incorporated herein by reference in their entireties and for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates to ligands for c-fms and c-kit, and to methods for use thereof. The information provided is intended solely to assist the understanding of the reader. None of the information provided nor references cited is admitted to be prior art to the present invention. Each of the references cited is incorporated herein in its entirety and for any purpose.

BACKGROUND OF THE INVENTION

[0003] C-fms and c-kit are both type III transmembrane receptor protein tyrosine kinases (RPTKs) that regulate key signal transduction cascades that control cellular growth and proliferation. Both receptors have similar structural features comprising five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment.

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c-Fms

[0004] C-fms is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses. The cellular proto-oncogene FMS (c-fms, cellular feline McDonough sarcoma) codes for the receptor for the macrophage colony-stimulating factor (M-CSF). C-fms is crucial for the growth and differentiation of the monocyte-macrophage lineage, and upon binding of M-CSF to the extracellular domain of c-fms, the receptor dimerizes and trans-autophosphorylates cytoplasmic tyrosine residues.

[0005] 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 levels of M-CSF in early pregnancy may participate in the immunologic mechanisms responsible for the maintenance of the pregnancy (Flanagan & Lader, Curr Opin Hematol. 1998, 5:181-5).

[0006] Related to c-fms and c-kit are two platelet-derived growth factor receptors, alpha (i.e., pdgfra) and beta (pdgfrb) (PDGF). The gene coding for pdgfra is located on chromosome 4q11-q12 in the same region of chromosome 4 as the oncogene coding for c-kit. The genes coding for pdgfra and c-fms appear to have evolved from a common ancestral gene by gene duplication, inasmuch as these two genes are tandemly linked on chromosome 5. They are oriented head-to-tail with the 5-prime exon of the c-fms gene located only 500 bp from the last 3-prime exon of the gene coding for pdgfra. Most gastrointestinal stromal tumors (GIST) have activating mutations in c-kit, and most patients with GISTs respond well to Gleevec, which inhibits c-kit. Heinrich et al. (Science 2003, 299:708-10) have shown that approximately 35% of GISTs lacking c-kit mutations have intragenic activation mutations in the gene encoding pdgfra, and that tumors expressing c-kit or pdgfra are indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, c-kit and pdgfra mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

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[0007] Similarly, the observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation points out a role for c-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 c-fms can ameliorate disease associated with increased levels of M-CSF.

c-Kit

[0008] The Stem Cell Factor (SCF) receptor c-kit plays an important role in the development of melanocytes and mast, germ and hematopoietic cells. Stem Cell Factor (SCF) is a protein encoded by the S1 locus, and has also been called "kit ligand" (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, Pathol Int 1996, 46:933-938; Loveland, et al., J. Endocrinol 1997, 153:337-344; Vliagoftis, et al., Clin Immunol 1997, 100:435-440; Broudy, Blood 1997, 90:1345-1364; Pignon, Hermatol Cell Ther 1997, 39:114-116; and Lyman, et al., Blood 1998, 91:1101-1134.). Herein the abbreviation SCF refers to the physiological ligand for c-kit.

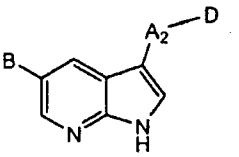
[0009] SCF is synthesized as a transmembrane protein with a molecular weight of 220 or 248 Dalton, depending on alternative splicing of the mRNA to encode exon 6. The larger protein can be proteolytically cleaved to form a soluble, glycosylated protein which noncovalently dimerizes. Both the soluble and membrane-bound forms of SCF can bind to and activate c-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 c-kit. In bone, marrow stromal cells express SCF and regulate hematopoiesis of c-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 c-kit on germ cells.

SUMMARY OF THE INVENTION

[0010] The present invention relates to compounds active on c-fms, c-kit, or both c-fms and c-kit. In accordance with one aspect of the present invention, it has been discovered that in the treatment of diseases amenable to treatment by an effective amount of a modulator of either c-fms alone or c-kit alone, the efficacy of treatment can be enhanced if said compounds are dual inhibitors of both c-fms and c-kit. In another aspect of the present invention, compounds active on c-fms, c-kit, or both c-fms and c-kit are also active on one or more of TrkA, TrkB and HGK. In particular, the invention provides compounds of Formula II, and all sub-generic formulae thereof

(e.g. Formula IIa, IIb, IIe, IIg and IIp), Formula III, or additional compounds as described in the synthetic examples, as well as methods of using such compounds as described below. Thus, the invention provides methods of using compounds that can be used therapeutically and/or prophylactically involving modulation of c-fms, c-kit, or both c-fms and c-kit, or involving one or more of TrkA, TrkB and HGK in addition to c-fms, c-kit, or both c-fms and c-kit.

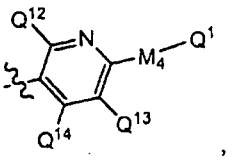
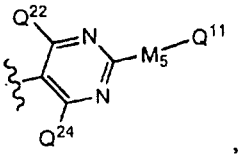
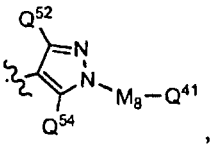
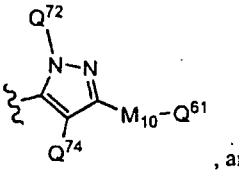
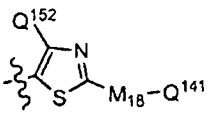
[0011] The compounds of Formula II have the following structure:



Formula II

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

D has a structure selected from the group consisting of  ,  ,  ,  , and 

in which  indicates the attachment point of D to A_2 of Formula II;

A_2 is $-CH_2-$ or -C(O)-;

B is selected from the group consisting of hydrogen, -CN, $-OR^{41}$, $-SR^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, $-C(O)NR^{39}R^{41}$, $-C(O)R^{41}$, $-S(O)_2NR^{39}R^{41}$, $-S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and

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heteroaryl as B, or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

M_4 is $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, or $-NR^{39}C(O)-$;

M_5, M_{10}, and M_{18} are selected from the group consisting of a bond, $-NR^{39}-$, -S-, -O-, $-NR^{39}CH_2-$, $-NR^{39}CH_2CH_2-$, $-NR^{39}CH(R^{40})-$, $-SCH_2-$, $-OCH_2-$, $-C(O)NR^{39}-$, $-S(O)_2NR^{39}-$, $-CH_2NR^{39}-$, $-CH(R^{40})NR^{39}-$, $-NR^{39}C(O)-$, and $-NR^{39}S(O)_2-$;

M_8 is selected from the group consisting of a bond, $-CH_2-$, $-CH_2C(O)-$, $-S(O)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2CH_2CH_2-$, $-S(O)_2NR^{39}-$, $-S(O)_2NR^{39}CH_2-$, $-S(O)_2NR^{39}CH(CH_3)-$, $-S(O)_2NR^{39}CH_2CH_2-$, $-C(O)-$, $-C(O)CH_2-$, $-C(O)CH(CH_3)-$, $-C(O)CH_2CH_2-$, $-C(O)NR^{39}-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, and $-C(O)NR^{39}CH_2CH_2-$;

Q^1 is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of Q^1 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{11}, Q^{41}, Q^{61}, and Q^{141} are lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein lower alkyl is optionally substituted with one or more fluoro, lower alkoxy, or fluoro substituted lower alkoxy, and wherein cyclaolkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of Q^{11}, Q^{41}, Q^{61}, or Q^{141}, or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of

-OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^{42}, -SR^{42}, -NHR^{42}, -$NR^{42}R^{42}$, -$NR^{39}C(O)R^{42}$, -$NR^{39}S(O)_2R^{42}$, -$S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{12} is fluoro, chloro or -CF_3;

Q^{13} and Q^{14} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl;

Q^{22}, Q^{24}, Q^{52}, and Q^{54} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, -$NR^{44}R^{44}$, -OR^{44}, and -SR^{44}, provided, however, that at least one of Q^{22} and Q^{24} and at least one of Q^{52} and Q^{54} is hydrogen, fluoro, chloro, lower alkyl or fluoro substituted lower alkyl;

Q^{74} and Q^{152} are hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, -$NR^{44}R^{44}$, -OR^{44}, or –SR^{44};

Q^{72} is hydrogen, lower alkyl or fluoro substituted lower alkyl;

R^{39} at each occurrence is independently hydrogen or lower alkyl;

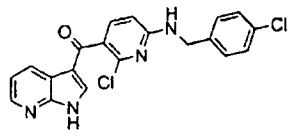
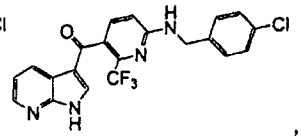
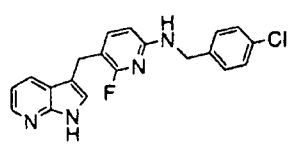
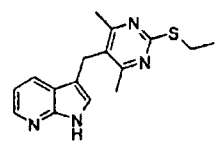
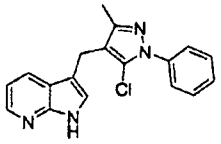
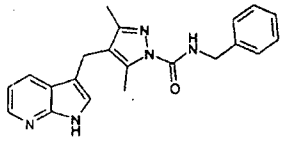
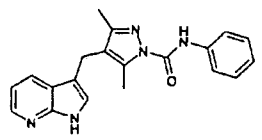
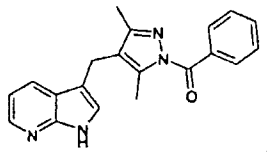
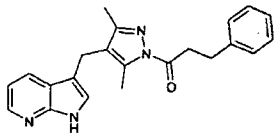
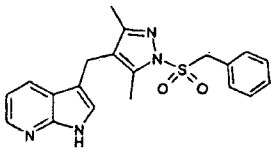
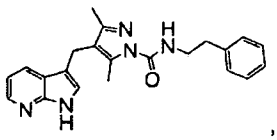
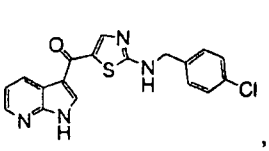
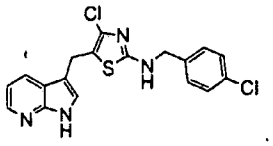
R^{40} is lower alkyl or fluoro substituted lower alkyl;

R^{41} at each occurrence is independently selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{41} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^{42}, -SR^{42}, -NHR^{42}, -$NR^{42}R^{42}$, -$NR^{39}C(O)R^{42}$, -$NR^{39}S(O)_2R^{42}$, -$S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

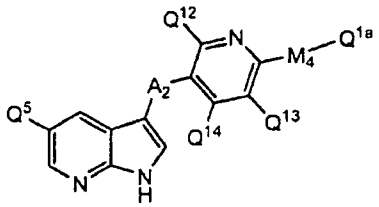
R^{42} at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy; and

each R^{44} is independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

provided, however, that the compound is not














, or

[0012] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIa,



Formula IIa,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

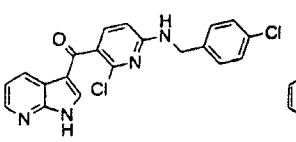
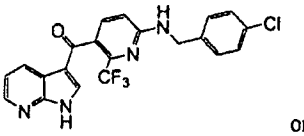
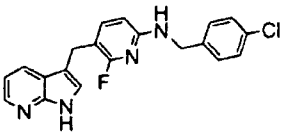
Q^{1a} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$;

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Q^5 is hydrogen, -CN, -OR^{41}, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, and -OR^{41}; and

A_2, M_4, Q^{12}, Q^{13}, Q^{14} and R^{41} are as defined for Formula II;

provided, however, that the compound is not



or


[0013] In one embodiment of compounds of Formula IIa, A_2 is -CH_2- and M_4 is -$NHCH_2$-. In one embodiment A_2 is -C(O)- and M_4 is -$NHCH_2$-. In one embodiment A_2 is -C(O)- and M_4 is -NHC(O)-. In one embodiment A_2 is -CH_2- and M_4 is -NHC(O)-.

[0014] In one embodiment of compounds of Formula IIa, A_2 is -CH_2-, M_4 is -$NHCH_2$-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0015] In one embodiment of compounds of Formula IIa, A_2 is -C(O)-, M_4 is -$NHCH_2$-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0016] In one embodiment of compounds of Formula IIa, A_2 is -C(O)-, M_4 is -NHC(O)-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0017] In one embodiment of compounds of Formula IIa, A_2 is -CH_2-, M_4 is -NHC(O)-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

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[0018] In one embodiment, further to any of the embodiments of Formula IIa above, R^{41} is R^{42} as defined for Formula II.

[0019] In one embodiment, further to any of the embodiments of Formula IIa above, Q^{1a} is phenyl or pyridinyl, wherein phenyl or pyridinyl are substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy and trifluoromethoxy; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; and Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy. In one embodiment, further to any of the embodiments of Formula IIa above, Q^{1a} is phenyl mono substituted with chloro, preferably at the 4-position; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; and Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy. In one embodiment, further to any of the embodiments of Formula IIa, Q^{1a} is pyridin-3-yl monosubstituted with methyl, methoxy, trifluoromethyl, difluoromethoxy or trifluoromethoxy, preferably at the 6-position; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy.

[0020] In one embodiment of compounds of Formula IIa, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is phenyl or pyridinyl, wherein phenyl or pyridinyl are substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy and trifluoromethoxy; Q^5 is hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -CN, or 1-methyl-1H-pyrazole-4-yl; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen. In one embodiment, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is phenyl mono substituted with chloro, preferably at the 4-position; Q^5 is hydrogen, chloro, methyl, methoxy, or -CN; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen. In one embodiment, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is pyridin-3-yl monosubstituted with methyl, methoxy, trifluoromethyl, difluoromethoxy or trifluoromethoxy, preferably at the 6-position; Q^5 is hydrogen, chloro, methyl, methoxy, -CN, or 1-methyl-1H-pyrazole-4-yl; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen.

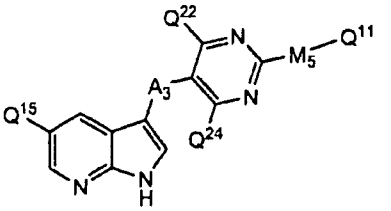
[0021] In one embodiment of compounds of Formula IIa, the compound is selected from the group consisting of:

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(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **(P-0132)**,
(4-Chloro-benzyl)-[6-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0161)**,
[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)**, and
all salts, prodrugs, tautomers, and isomers thereof.

[0022] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIb,

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Formula IIb,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_3 is $-CH_2-$ or $-C(O)-$;

Q^{15} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_5, Q^{11}, Q^{22}, Q^{24}, and R^{41}, are as defined for Formula II.

[0023] In one embodiment of compounds of Formula IIb, M_5 is $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, or $-NR^{39}C(O)-$; A_3 is $-CH_2-$ or $-C(O)-$, preferably $-CH_2-$; Q^{11} is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and Q^{22} and Q^{24} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen, fluoro, chloro, or $-CF_3$, more preferably both Q^{22} and Q^{24} are hydrogen; wherein R^{41} is as defined for Formula II.

[0024] In one embodiment, further to any of the embodiments of Formula IIb above, R^{41} is R^{42} as defined for Formula II.

[0025] In one embodiment of compounds of Formula IIb, M_5 is $-NHCH_2CH_2-$, $-NHCH_2-$ $-N(CH_3)CH_2-$, or $-NHCH(CH_3)-$, preferably $-NHCH_2-$; A_3 is $-CH_2-$; Q^{11} is cycloalkyl, heterocycloalkyl, phenyl or heteroaryl, wherein phenyl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, lower alkyl, fluoro

substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, di-alkylamino, and heterocycloalkyl; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and Q^{22} and Q^{24} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen, fluoro, chloro, or $-CF_3$, more preferably both Q^{22} and Q^{24} are hydrogen.

[0026] In one embodiment of compounds of Formula IIb, M_5 is $-NHCH_2-$; A_3 is $-CH_2-$; Q^{11} is phenyl substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, fluoro substituted methyl, methoxy, and fluoro substituted methoxy; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, preferably hydrogen or chloro; and Q^{22} and Q^{24} are hydrogen.

[0027] In one embodiment of compounds of Formula IIb, the compound is selected from the group consisting of:

(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0260)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,6-difluoro-benzyl)-amine **(P-0261)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0262)**,

(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0263)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine **(P-0264)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine **(P-0265)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine **(P-0266)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine **(P-0267)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine **(P-0268)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-

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benzyl)-amine **(P-0289)**,
(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0291)**,
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0292)**,
(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0293)**,
(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0294)**,
(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0295)**,
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0300)**,
(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0301)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0302)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine **(P-0303)**,
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0304)**,
(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0305)**,
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0306)**,
(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0307)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine **(P-0308)**,
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0309)**,
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0310)**,
(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0311)**,
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0312)**,
(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0313)**,
(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0314)**,
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0315)**,
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0316)**,

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(5-Chloro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0317)**,

(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0318)**,

(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0319)**,

(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0320)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine **(P-0390)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-trifluoromethyl-benzyl)-amine **(P-0391)**,

(3-Chloro-2-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0392)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-3-trifluoromethyl-benzyl)-amine **(P-0393)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-4-trifluoromethyl-benzyl)-amine **(P-0394)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,3-difluoro-benzyl)-amine **(P-0395)**,

(2-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0396)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine **(P-0402)**,

(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0407)**,

(2-Chloro-5-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0408)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine **(P-0416)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-pyrrolidin-1-yl-ethyl)-amine **(P-0417)**,

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0418)**,

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine **(P-0419)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethoxy-benzyl)-

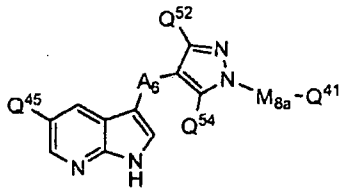
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amine (**P-0420**),
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0421**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-0422**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-benzyl)-amine (**P-0423**),
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0424**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,5-difluoro-benzyl)-amine (**P-0425**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(2-fluoro-phenyl)-ethyl]-amine (**P-0426**),
[1-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0427**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-0428**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0429**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0430**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methyl-benzyl)-amine (**P-0431**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-benzyl)-amine (**P-0433**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-ethyl)-amine (**P-0434**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexylmethyl-amine (**P-0435**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-0436**),
[2-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0437**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-difluoromethoxy-benzyl)-amine (**P-0438**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methoxy-benzyl)-amine

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(**P-0439**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-benzyl)-amine (**P-0440**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-ethyl)-amine (**P-0441**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-benzyl)-amine (**P-0442**),
(3-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0443**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-ethoxy-benzyl)-amine (**P-0444**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-morpholin-4-yl-benzyl)-amine (**P-0445**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-difluoromethoxy-benzyl)-amine (**P-0446**),
(4-Chloro-3-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0447**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(3-fluoro-phenyl)-ethyl]-amine (**P-0448**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-dimethylamino-benzyl)-amine (**P-0449**), and
all salts, prodrugs, tautomers, and isomers thereof.

[0028] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIe,



Formula IIe,

all salts, prodrugs, tautomers, and isomers thereof,
wherein:

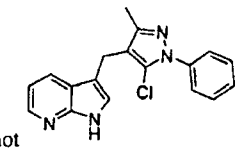
A_6 is $-CH_2-$ or $-C(O)-$;

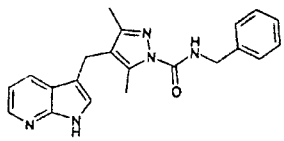
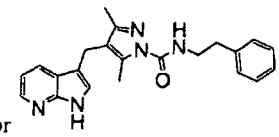
M_{8a} is $-CH_2-$, $-CH_2C(O)-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(R^{40})-$, or $-C(O)NR^{39}CH_2CH_2-$;

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Q^{45} is hydrogen, -CN, -OR^{41}, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, and -OR^{41}; and

Q^{41}, Q^{52}, Q^{54}, R^{39}, R^{40}, and R^{41} are as defined for Formula II;

provided, however, that the compound is not  ,

 , or  .

[0029] In one embodiment of compounds of Formula IIe, M_{8a} is -$C(O)NR^{39}CH_2$-, -$C(O)NR^{39}CH(CH_3)$-, or -$C(O)NR^{39}(CH_2)_2$-; A_6 is -CH_2- or -C(O)-, preferably -CH_2-; Q^{41} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; Q^{45} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{52} and Q^{54} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably Q^{52} and Q^{54} are independently hydrogen, fluoro, chloro, methyl, or -CF_3; wherein R^{41} is as defined in Formula II.

[0030] In one embodiment, further to any of the embodiments of Formula IIe above, R^{41} is R^{42} as defined for Formula II.

[0031] In one embodiment of compounds of Formula IIe, M_{8a} is -$C(O)NHCH_2$-, -$C(O)NHCH(CH_3)$- or -$C(O)NH(CH_2)_2$-; A_6 is -CH_2- or -C(O)-, preferably -CH_2-; Q^{41} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, fluoro substituted methyl, methoxy, and fluoro substituted methoxy; Q^{45} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen or chloro; and Q^{52} and

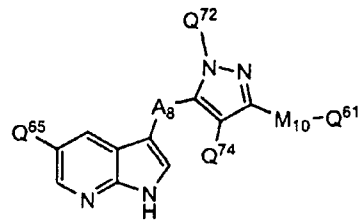
Q^{54} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably Q^{52} and Q^{54} are methyl.

[0032] In one embodiment of compounds of Formula IIe, the compound is selected from the group consisting of:
3-(1-Benzyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **(P-0133)**,
2-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-1-phenyl-ethanone **(P-0134)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide **(P-0135)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-chloro-benzylamide **(P-0136)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-fluoro-benzylamide **(P-0137)**,
3-[3,5-Dimethyl-1-(5-trifluoromethyl-furan-2-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0138)**,
3-[3,5-Dimethyl-1-(5-methyl-isoxazol-3-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0139)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-chloro-benzylamide **(P-0140)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide **(P-0141)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-methoxy-benzylamide **(P-0142)**,
3-{3,5-Dimethyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-pyrazol-4-ylmethyl}-1H-pyrrolo[2,3-b]pyridine **(P-0143)**,
3-[3,5-Dimethyl-1-(4-methyl-2-phenyl-thiazol-5-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0144)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methoxy-benzylamide **(P-0145)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide **(P-0146)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide **(P-0147)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide **(P-0148)**,

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3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid ((S)-1-phenyl-ethyl)-amide **(P-0149)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-fluoro-benzylamide **(P-0150)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-fluoro-benzylamide **(P-0151)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methyl-benzylamide **(P-0152)**,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methyl-benzylamide **(P-0153)**,
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide **(P-0157)**,
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-fluoro-benzylamide **(P-0158)**,
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-chloro-benzylamide **(P-0159)**,
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [(S)-1-(4-fluoro-phenyl)-ethyl]-amide **(P-0160)** , and
all salts, prodrugs, tautomers, and isomers thereof.

[0033] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIg,



Formula IIg,

all salts, prodrugs, tautomers, and isomers thereof,
wherein:

A_8 is $-CH_2-$, or -C(O)-;

Q^{65} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the

group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_{10}, Q^{61}, Q^{72}, Q^{74}, and R^{41} are as defined for Formula II.

[0034] In one embodiment of compounds of Formula IIg, M_{10} is $-NR^{39}CH_2-$ or $-NR^{39}-(CH_2)_2-$; A_8 is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{61} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; Q^{65} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and Q^{74} is hydrogen, fluoro, chloro, lower alkyl or fluoro substituted lower alkyl, wherein R^{41} is as defined for Formula II.

[0035] In one embodiment, further to any of the embodiments of Formula IIg above, R^{41} is R^{42} as defined for Formula II.

[0036] In one embodiment of compounds of Formula IIg, M_{10} is $-NHCH_2-$; A_8 is $-CH_2-$; Q^{61} is phenyl optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy or trifluoromethoxy; Q^{65} is hydrogen, fluoro, -CN, or 1-methyl-pyrazol-4-yl; Q^{72} is lower alkyl or fluoro substituted lower alkyl; and Q^{74} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl. In one embodiment, M_{10} is $-NHCH_2-$; A_8 is $-CH_2-$; Q^{61} is 4-fluoro-phenyl; Q^{65} is hydrogen, chloro, -CN, or 1-methyl-pyrazol-4-yl; Q^{72} is methyl or ethyl; and Q^{74} is hydrogen or chloro.

[0037] In one embodiment, the compound of Formula IIg is selected from the group consisting of:

[1-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0165)**,

(4-Fluoro-benzyl)-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-amine **(P-0169)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0170)**,

(4-Fluoro-benzyl)-{1-methyl-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-1H-pyrazol-3-yl}-amine **(P-0180)**,

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-

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methanone **(P-0184)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0185)**,

3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0191)**,

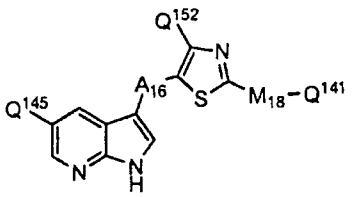
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine **(P-0410)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2,5-difluoro-benzyl)-amine **(P-0411)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2-fluoro-benzyl)-amine **(P-0413)**, and

all salts, prodrugs, tautomers, and isomers thereof.

[0038] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIp,



Formula IIp,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

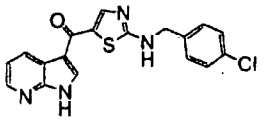
A_{16} is $-CH_2-$ or $-C(O)-$;

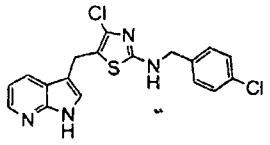
Q^{145} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$;

Q^{152} is hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy; and

M_{16}, Q^{141}, and R^{41}, are as defined for Formula II;

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provided, however, that the compound is not  or



[0039] In one embodiment of compounds of Formula IIp, M_{18} is $-NR^{39}CH_2-$ or $-NR^{39}-(CH_2)_2-$; A_{16} is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{141} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; Q^{145} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and Q^{152} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl; wherein R^{41} is as defined for Formula II.

[0040] In one embodiment of compounds of Formula IIp, M_{18} is $-NH-CH_2-$ or $-NH-(CH_2)_2-$, preferably $-NH-CH_2-$; A_{16} is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{141} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, and heterocycloalkyl; Q^{145} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen, -CN, or chloro; and Q^{152} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen or chloro, more preferably chloro.

[0041] In one embodiment, the compound of Formula Ih is selected from the group consisting of
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0156)**,
[4-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0162)**,
(4-Fluoro-benzyl)-[4-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0163)**,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine **(P-0164)**,

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[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-2-ylmethyl-amine **(P-0167)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine **(P-0168)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine **(P-0171)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amine **(P-0172)**,

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

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amine**(P-0175)**,

{2-(4-Fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **(P-0177)**,

{2-[(4-Chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **(P-0178)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-thiazol-2-ylmethyl-amine **(P-0189)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0190)**,

Benzyl-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0192)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine **(P-0193)**,

(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0194)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0195)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine **(P-0196)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine **(P-0197)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-2H-pyrazol-3-ylmethyl)-amine **(P-0198)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine **(P-0199)**,

[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]-(2-methyl-thiazol-4-ylmethyl)-amine **(P-0201)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-methyl-thiazol-5-ylmethyl)-amine **(P-0202)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-chloro-pyridin-2-ylmethyl)-amine **(P-0203)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine **(P-0204)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine **(P-0205)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine **(P-0206)**,

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

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4,5-dimethyl-thiophen-2-ylmethyl)-amine **(P-0208)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-thiophen-3-ylmethyl)-amine **(P-0209)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **(P-0231)**,

[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]-pyridin-4-ylmethyl-amine **(P-0237)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-chloro-pyridin-4-ylmethyl)-amine **(P-0238)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1-ethyl-1H-pyrazol-4-ylmethyl)-amine **(P-0239)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine **(P-0240)**,

[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-chloro-6-fluoro-benzyl)-amine **(P-0243)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-phenethyl-amine **(P-0244)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-difluoro-benzyl)-amine **(P-0245)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-fluoro-benzyl)-amine **(P-0246)**,

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

(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0248)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine **(P-0249)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine **(P-0250)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-2-ylmethyl)-amine **(P-0251)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine **(P-0252)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3,5-dichloro-pyridin-4-ylmethyl)-amine **(P-0253)**,

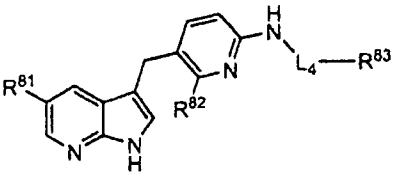
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0254)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine **(P-0255)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0290)** , and

all salts, prodrugs, tautomers, and isomers thereof.

[0042] The compounds of Formula III have the following structure:



Formula III,

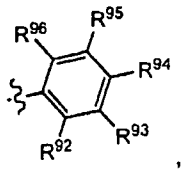
all salts, prodrugs, tautomers, and isomers thereof,

wherein:

L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, -C(O)- or -C(O)NH-;

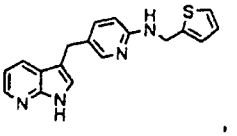
R^{81} is selected from the group consisting of hydrogen, $-OR^{41}$, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

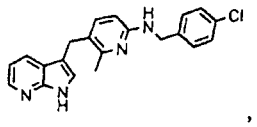
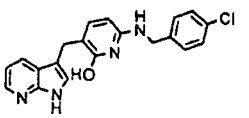
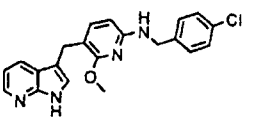
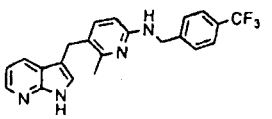
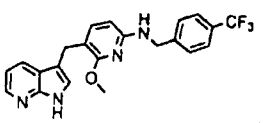
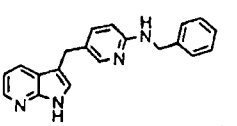
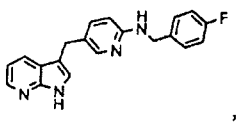
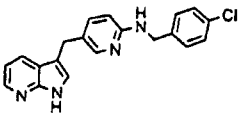
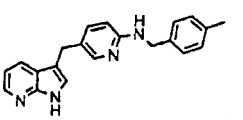
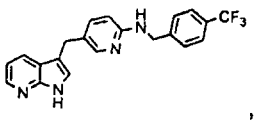
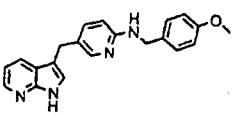
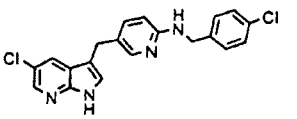
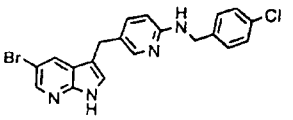
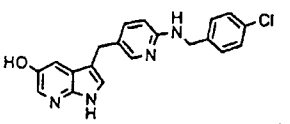
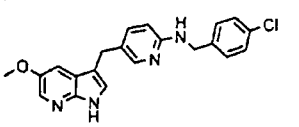
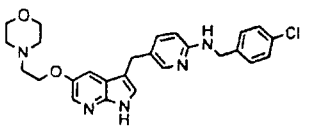
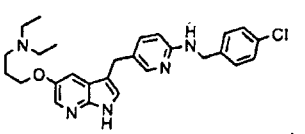
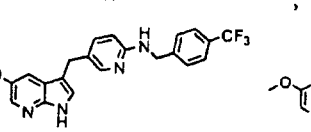
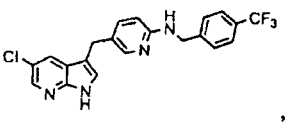
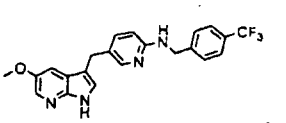
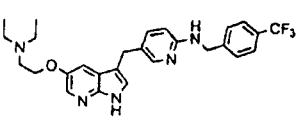
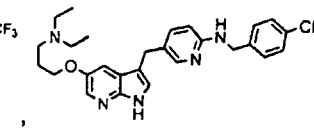
R^{82} is selected from the group consisting of hydrogen, C_{1-3} alkyl, fluoro substituted C_{2-3} alkyl, OH, C_{1-3} alkoxy, and fluoro substituted C_{1-3} alkoxy;

R^{83} is heterocycloalkyl, heteroaryl, or  , in which  indicates the attachment point of R^{83} to L_4 of Formula III, wherein heterocycloalkyl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

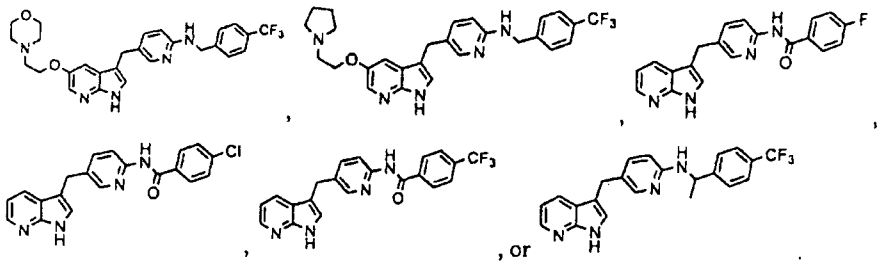
R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and

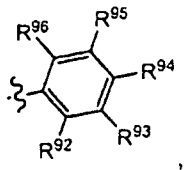
R^{40} and R^{41} are as defined for Formula II;

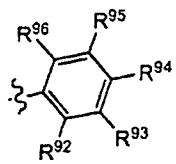
provided, however, that the compound is not 

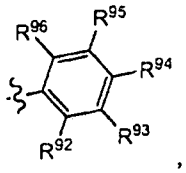

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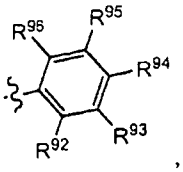


[0043] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or -C(O)-; R^{81} is hydrogen, fluoro, chloro, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy; R^{82} is hydrogen; R^{83} is  , wherein R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, provided, however, that when R^{94} is fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, at least one of R^{92}, R^{93}, R^{95}, and R^{96} is fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy.

[0044] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or -C(O)-; R^{81} is hydrogen, fluoro, chloro, -CN, methyl, or methoxy, preferably hydrogen, chloro, -CN, or methyl; R^{82} is hydrogen; R^{83} is  , wherein R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy, preferably hydrogen, chloro, methyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy, provided, however, that when R^{94} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy, at least one of R^{92}, R^{93}, R^{95}, and R^{96} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy.

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[0045] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$; R^{81} is fluoro, chloro, -CN, methyl, or methoxy, preferably chloro, -CN, or methyl; R^{82} is hydrogen; R^{83} is  , wherein R^{94} is hydrogen and R^{92}, R^{93}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy.

[0046] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, -C(O)-, or $-CH(CH_3)-$, preferably $-CH_2-$ or -C(O)-; R^{81} is hydrogen or flouro; R^{82} is hydrogen; R^{83} is  , wherein R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, methyl, or trifluoromethyl, and R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy or trifluoromethoxy, preferably hydrogen or fluoro. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; and R^{93}, R^{94}, R^{95}, and R^{96} are hydrogen. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; R^{94}, R^{95}, and R^{96} are hydrogen; and R^{93} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, trifluoromethyl or methoxy, more preferably fluoro. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; R^{93}, R^{95}, and R^{96} are hydrogen; and R^{94} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, methyl or trifluoromethyl, more preferably fluoro. In one embodiment, L_4 is $-CH_2CH_2-$ or -C(O)-; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{95}, and R^{96} are hydrogen; R^{93} is hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, or trifluoromethoxy, more preferably fluoro, chloro, trifluoromethyl or methoxy; and R^{94} is hydrogen, fluoro, or chloro; provided, however, that when L_4 is -C(O)- and R^{94} is fluoro or chloro, R^{93} is not hydrogen. In one

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embodiment, L_4 is $-CH_2CH_2-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{94}, R^{95}, and R^{96} are hydrogen; and R^{93} is hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably hydrogen or fluoro. In one embodiment, L_4 is $-C(O)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{95}, and R^{96} are hydrogen; R^{93} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, trifluoromethyl or methoxy; and R^{94} is hydrogen, fluoro, or chloro.

[0047] In one embodiment of compounds of Formula III, R^{83} is pyrrolidine, morpholine, pyridine, pyrimidine, pyrazine, pyrazole, isoxazole, imidazol, or benzimidazole, wherein R^{83} is optionally substituted with one or more substituents independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$, preferably wherein R^{83} is optionally substituted with 1 or 2 substituents independently selected from fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, or cycloalkylamino, more preferably fluoro, chloro, methyl, trifluoromethyl, methoxy or morpholine.

[0048] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or $-C(O)-$, preferably $-CH_2-$, $-CH_2CH_2-$, or $-C(O)-$; R^{81} is hydrogen, fluoro, chloro, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen, chloro, methyl or -CN; R^{82} is hydrogen; and R^{83} is pyrrolidine, morpholine, pyridine, pyrimidine, pyrazine, pyrazole, isoxazole, imidazole, or benzimidazole, wherein R^{83} is optionally substituted with 1 or 2 substituents independently selected from fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, or cycloalkylamino, preferably fluoro, chloro, methyl, trifluoromethyl, methoxy or morpholine.

[0049] In one embodiment of compounds of Formula III, the compound is selected from the group consisting of:

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

(5-Methyl-isoxazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0095)**,

(2-Pyrrolidin-1-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0096)**,

[1-(4-Methanesulfonyl-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0097)**,

(2-Morpholin-4-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0099)**,

3,4-Dichloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **(P-0100)**,

2-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **(P-0101)**,

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-

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yl]-amide (**P-0102**),
Thiophene-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0103**),
2-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0104**),
N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0105**),
Pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0106**),
Pyridine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0107**),
6-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-nicotinamide (**P-0108**),
4-Fluoro-3-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0109**),
5-Methyl-pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0110**),
3-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0111**),
4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0112**),
N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethoxy-benzamide (**P-0113**),
N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0114**),
3-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0115**),
3,4-Difluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0116**),
2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0117**),
5-Fluoro-2-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0118**),
2-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0119**),
3-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0120**),
3-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0121**),
3-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0122**),
2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0123**),
((R)-1-Phenyl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0125**),
(3-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0126**),
[1-(2-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0127**),
[2-(3-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

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(P-0128),
(3-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0129),
(1-Methyl-1H-imidazol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0130),
(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0131),
[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),
(3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0183),
(2-Chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0210),
Phenethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0211),
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0212),
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0213),
(3-Bromo-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0214),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0215),
(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0216),
(2-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0217),
(1-Methyl-1H-benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0218),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0219),
(1H-Benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0220),
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0221),
(5-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0222),
(3-Fluoro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0223),
(6-Methoxy-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

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(P-0224),
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0225)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0226)**,
(3,5-Dichloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0227)**,
(6-Morpholin-4-yl-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0228)**,
(3-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0229)**,
(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0230)**,
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0235)**,
3-{6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0256)**,
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0257)**,
Propane-1-sulfonic acid (2,4-difluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide **(P-0258)**,
Propane-1-sulfonic acid (3-{[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-2,4-difluoro-phenyl)-amide **(P-0259)**,
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0269)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine **(P-0270)**,
3-[6-(2-Fluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0271)**,
(2-Fluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0272)**,
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0273)**,
3-[6-(2-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0274)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-

amine **(P-0275)**,
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0276)**,
3-[6-(2,6-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0277)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine **(P-0278)**,
(2-Chloro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0279)**,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0280)**,
3-[6-(2-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0281)**,
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0282)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0283)**,
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)**,
(2-Ethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0288)**,
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0296)**,
(2,5-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0297)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,5-difluoro-benzyl)-amine **(P-0298)**,
3-[6-(2,5-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0299)**,
3-[6-(2-Trifluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0321)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethoxy-benzyl)-amine

(P-0322),
3-[6-(2-Ethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0323),
[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]-(2-trifluoromethyl-benzyl)-amine (P-0325),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (P-0326),
(2-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0327),
(2-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0328),
(2,5-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0329),
(2,5-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0330),
[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),
(2,6-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0333),
(2,6-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0334),
(2-Methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0336),
3-[6-(2-Methoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0337),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-difluoromethoxy-benzyl)-amine (P-0338),
3-[6-(2-Difluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0339),
(2,6-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0340),
(2,6-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0341),
(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0342),

(3-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0343)**,
(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0344)**,
(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0345)**,
(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0346)**,
(2-Morpholin-4-yl-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0347)**,
(4-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0348)**,
(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0349)**,
(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0350)**,
(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0351)**,
(2-Fluoro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0352)**,
Dimethyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine **(P-0353)**,
(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0354)**,
(5-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0355)**,
(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0356)**,
(2-Propoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0357)**,
(2-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0358)**,
(2-Chloro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0359)**,
(2-Fluoro-6-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0360)**,
[2-(2-Morpholin-4-yl-ethoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0361)**,
(2,3-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0362)**,
(2-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-

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amine **(P-0363)**,
(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0364)**,
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0365)**,
(5-Fluoro-2-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0366)**,
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0367)**,
(2-Fluoro-4-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0368)**,
[2-(3-Dimethylamino-propoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0369)**,
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0370)**,
(2-Fluoro-5-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0371)**,
(4-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0372)**,
(3-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0373)**,
(6-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0374)**,
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0375)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine **(P-0376)**,
Propane-1-sulfonic acid (2-fluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide **(P-0377)**,
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0380)**,
Pyrimidin-5-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0381)**,
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0382)**,
(2-Ethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0383)**,
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)**,
Methyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine **(P-0386)**,
(2-Chloro-4-methanesulfonyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0387)**,
Possibly to be added (P-0388),
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0397)**,
Dimethyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine **(P-0399)**,
(5-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0400)**,
(2-Methoxy-pyrimidin-5-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0401)**,
[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)**,
1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea **(P-0412)** , and all salts, prodrugs, tautomers, and isomers thereof.

[0050] In one embodiment, a compound of the invention is:
(4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine **(P-0092)**,
(4-Morpholin-4-ylmethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0093)**,
(2-Methoxy-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0098)**,
[4-Chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine **(P-0166)**,
((2,2-Difluoro-benzo[1,3]dioxol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0398)**; or
any salts, prodrugs, tautomers, and isomers thereof.

[0051] In certain embodiments of the above compounds, compounds are excluded where N (except where N is a heteroaryl ring atom), O, or S is bound to a carbon that is also bound to N (except where N is a heteroaryl ring atom), O, or S, except where the carbon forms a double bond with one of the heteroatoms, such as in an amide, carboxylic acid, and the like; or where N (except where N is a heteroaryl ring atom), O, C(S), C(O), or $S(O)_n$ (n is 0-2) is bound to an alkene carbon

of an alkenyl group or bound to an alkyne carbon of an alkynyl group; accordingly, in certain embodiments compounds which include linkages such as the following are excluded from the present invention: -NR-CH_2-NR-, -O-CH_2-NR-, -S-CH_2-NR-, -NR-CH_2-O-, –O-CH_2-O-, -S-CH_2-O-,–NR-CH_2-S-, –O-CH_2-S-, –S-CH_2-S-, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, -$S(O)_{0-2}$-CH=CH-, -CH=CH-$S(O)_{0-2}$-, –$S(O)_{0-2}$-C≡C-, -C≡C-$S(O)_{0-2}$-, –C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, or -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, or -C(S)-C≡C-.

[0052] In reference to compounds herein, specification of a compound or group of compounds includes pharmaceutically acceptable salts of such compound(s), prodrug(s), and all stereoisomers, unless clearly indicated to the contrary. In reference to compounds of Formula II, it is understood that such reference includes compounds of Formulae IIa, IIb, IIe, IIg and IIp, and all sub-embodiments thereof.

[0053] In another aspect, the invention provides methods for treating a c-kit-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-kit-mediated disease or condition an effective amount of a compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the c-kit mediated disease is selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including, but not limited to, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

[0054] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-kit-mediated disease or condition selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic

leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including, but not limited to, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

[0055] In a further aspect, the invention provides methods for treating a c-fms-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-fms activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-fms-mediated disease or condition an effective amount of compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the c-fms mediated disease is selected from the group consisting of immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection; inflammatory diseases including, but not limited to, osteoarthritis, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, 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, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; 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, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

[0056] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-fms-mediated disease or condition selected from the group consisting of immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection;

inflammatory diseases including, but not limited to, osteoarthritis, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, 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, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; 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, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

[0057] In a further aspect, the invention provides methods for treating, in an animal subject (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), a disease or condition mediated by c-fms and c-kit, e.g., a disease or condition characterized by abnormal c-fms activity and c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a disease or condition mediated by c-fms and c-kit an effective amount of compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the condition mediated by c-fms and c-kit is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage

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activation syndrome), multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

[0058] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a disease or condition mediated by c-fms and c-kit selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

[0059] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on Ret, PDGF, or both Ret and PDGF. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on c-fms. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-fms than on c-kit. In certain embodiments, the

compound has in combination each pairing of activity (e.g. IC_{50}) and/or selectivity as specified in this paragraph.

[0060] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for c-kit, c-fms, or both c-kit and c-fms kinase activity. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit, c-fms, or both c-kit and c-fms than on Ret, PDGF, or both Ret and PDGF.

[0061] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for c-kit, c-fms, or both c-kit and c-fms kinase activity, and further has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for at least one of HGK, TrkA, or TrkB kinase activity.

[0062] An additional aspect of this invention relates to compositions that include a therapeutically effective amount of a compound of Formula II or Formula III and all sub-embodiments thereof and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds of Formula II or Formula III. The composition can further include one or more different pharmacologically active compounds, which can include one or more compounds of Formula II or Formula III.

[0063] In one aspect, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including a compound of Formula II or Formula III, 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 aspect, 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,

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adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexafin lutetium), surgery, and bone marrow and stem cell transplantation.

[0064] In one aspect, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including a compound of Formula II or Formula III, in combination with one or more suitable chemotherapeutic agents. In one aspect, the one or more suitable chemotherapeutic agents is selected from an alkylating agent, including, but not limited to, 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; an antibiotic, including, but not limited to, 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; an immunotherapy, including, but not limited to, 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; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, 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, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; a kinase inhibitor, including, but not limited to, 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; 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), aminoglutethimide, asparaginase, bryostatin-1, cilengitide, E7389, ixabepilone, procarbazine, sulindac, temsirolimus,

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tipifarnib. Preferably, the method of treating a cancer involves administering to the subject an effective amount of a composition of Formula II, Formula III or Formula IV in combination with a chemotherapeutic agent selected from 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, or erlotinib.

[0065] In another aspect, the invention provides a method of treating or prophylaxis of a disease or condition in a mammal, by administering to the mammal a therapeutically effective amount of a compound of Formula II or Formula III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug. The compound can be alone or can be part of a composition.

[0066] In a related aspect, the invention provides kits that include a composition as described herein. In particular embodiments, the composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the 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 composition is approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the kit of the invention includes written instructions on use and/or other indication that the composition is suitable or approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the composition is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0067] In another aspect, the present invention also provides a method for modulating c-kit or c-fms activity by contacting c-kit or c-fms with an effective amount of a compound of Formula II or Formula III and all sub-embodiments thereof active on c-kit and/or c-fms (such as compounds developed using methods described herein). The compound is preferably provided at a level sufficient to modulate the activity of the c-kit or c-fms by at least 10%, more preferably at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater than 90%. In many embodiments, the compound will be at a concentration of about 1 μM, 100 μM, or 1 mM, or in a range of 1-100 nM, 100-500 nM, 500-1000 nM, 1-100 μM, 100-500 μM, or 500-1000 μM. In particular embodiments, the contacting is carried out *in vitro*.

[0068] Additional aspects and embodiments will be apparent from the following Detailed Description and from the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0069] As used herein the following definitions apply:

[0070] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0071] "Hydroxyl" and "hydroxy" refer to the group -OH.

[0072] "Thiol" refers to the group -SH.

[0073] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. "Optionally substituted lower alkyl" denotes lower alkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, 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. While it is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted alkyl is an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution of the alkyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the substituent (except where -N- is a heteroaryl ring atom) being bound to the alkyl carbon bound to any -O-, -S-, or -N- of the moiety.

[0074] "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. A "substituted cycloalkyl" is a cycloalkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0075] "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.

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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 one of the ring carbons is 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. A "substituted heterocycloalkyl" is a heterocycloalkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0076] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members. A "substituted aryl" is an aryl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0077] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. A "substituted heteroaryl" is a heteroaryl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0078] "Lower alkoxy" denotes the group $-OR^z$, where R^z is lower alkyl. "Substituted lower alkoxy" denotes lower alkoxy in which R^z is lower alkyl substituted with one or more substituents as indicated herein attached at any available atom to produce a stable compound. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on

alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that -O-, -S-, or –N- (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy -O-. Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0079] "Lower alkylthio" denotes the group $-SR^{aa}$, where R^{aa} is lower alkyl. "Substituted lower alkylthio" denotes lower alkylthio in which R^{aa} is lower alkyl substituted with one or more substituents as indicated herein attached at any available atom to produce a stable compound. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkylthio are attached at any available atom to produce a stable compound, substitution of alkylthio is such that -O-, -S-, or –N- (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkylthio -S-. Further, where alkylthio is described as a substituent of another moiety, the alkylthio sulfur is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0080] "Mono-alkylamino" denotes the group $-NHR^{bb}$ where R^{bb} is lower alkyl. "Di-alkylamino" denotes the group $-NR^{bb}R^{cc}$, where R^{bb} and R^{cc} are independently lower alkyl. "Cycloalkylamino" denotes the group $-NR^{dd}R^{ee}$, where R^{dd} and R^{ee} combine with the nitrogen to form a 5-7 membered heterocycloalkyl, 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. While it is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties that are attached at any available atom to produce a stable compound, the nitrogen of mono-alkylamino, di-alkylamino, or cycloalkylamino as substituents is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety.

[0081] As used herein, the term c-kit-mediated disease or condition refers to a disease or condition in which the biological function of c-kit affects the development and/or course of the disease or condition, and/or in which modulation of c-kit alters the development, course, and/or symptoms. For example, mutations in the c-kit gene such as the W42, Wv, and W41 mutations

reported by Herbst et al al (J. Biol. Chem., 1992, 267: 13210-13216) confer severe, intermediate, and mild phenotypic characteristics, respectively. These mutations attenuate the intrinsic tyrosine kinase activity of the receptor to different degrees and are models for the effect of modulation of c-kit activity. A c-kit mediated disease or condition includes a disease or condition for which c-kit inhibition provides a therapeutic benefit, e.g. wherein treatment with c-kit inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0082] As used herein, the term c-fms-mediated disease or condition refers to a disease or condition in which the biological function of c-fms affects the development and/or course of the disease or condition, and/or in which modulation of c-fms alters the development, course, and/or symptoms. For example, the *Csf1r*$^{-}$/*Csf1r*$^{-}$ mutant mouse of Dai et al (Blood, 2002, 99: 111-120) which lacks c-fms is an animal model for diseases or conditions wherein c-fms activity has been abolished. A c-fms mediated disease or condition includes a disease or condition for which c-fms inhibition provides a therapeutic benefit, e.g. wherein treatment with c-fms inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0083] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0084] 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.

[0085] In the present context, the terms "therapeutically effective" and "effective amount" indicate 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.

[0086] 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 c-kit or c-fms. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme.

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[0087] The term "c-kit activity" refers to a biological activity of c-kit, particularly including kinase activity. The term "c-fms activity" refers to a biological activity of c-fms, particularly including kinase activity.

I. General

[0088] In one aspect, the present invention concerns compounds of Formula II, IIa, IIb, IIe, IIg, IIp or III and all sub-embodiments thereof, that are inhibitors of c-kit, c-fms, or both c-kit and c-fms, and the use of the compounds in treating diseases that are mediated by c-kit, c-fms, or both c-kit and c-fms.

Exemplary Diseases Associated with c-Kit.

[0089] The compounds described herein are useful for treating disorders related to c-kit e.g., diseases related to unregulated kinase signal transduction, including cell proliferative disorders, fibrotic disorders and metabolic disorders, among others. As described in more detail below and in Lipson et al., U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003) which is incorporated herein by reference in its entirety, cell proliferative disorders which can be treated by the present invention include cancers, and mast cell proliferative disorders.

[0090] The presence of c-kit has also been associated with a number of different types of cancers. In addition, the association between abnormalities in c-kit and disease are not restricted to cancer. As such, c-kit has been associated with malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

Exemplary diseases associated with c-fms

[0091] The presence of c-fms has been associated with a number of different types of diseases. As such, c-fms has been associated with immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection; inflammatory diseases including, but not limited to, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, 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, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g., osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; 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. diapetic nephropathy), and renal hypertrophy; disorders of the central nervous system, including, but not limited to, multiple sclerosis, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

Exemplary diseases associated with TrkA and TrkB

[0092] TrkA: Target kinase TrkA (i.e., neurotrophic tyrosine kinase, receptor, type 1) is a 140 kDa tyrosine kinase encoded by chromosome 1q21-q22 (symbol: NTRK1). TrkA inhibitors may be useful in treating pain (e.g. chronic pain, neuropathic pain), cancer (e.g. prostate cancer, lung cancer, myeloid leukemia, pancreatic cancer), arthritis, allergic disorders (e.g. asthma), diabetic retinopathy, macular degeneration and psoriasis.

[0093] TrkB: Target kinase TrkB (i.e., neurotrophic tyrosine kinase, receptor, type 2) is a 145 kDa tyrosine kinase encoded by chromosome 9q22.1 (symbol: NTRK2). TrkB inhibitors may be useful in treating various cancers and their metastases (e.g. prostate cancer, lung cancer, Wilm's tumors, neuroblastoma, and pancreatic cancer), and various neuropathies (e.g. stroke, multiple sclerosis, transverse myelitis, and encephalitis).

Exemplary diseases associated with HGK

[0094] HGK: Target kinase HGK (i.e., Hematopoietic progenitor kinase/Germinal center kinase-like Kinase, aka mitogen-activated protein kinase kinase kinase kinase 4) is a 130 kDa serine/threonine kinase encoded by chromosome 2q11.2-q12 (symbol: MAP4K4). HGK inhibitors may be useful in treating metabolic indications, including re-sensitizing fat and muscle cells to insulin, ameliorating the pathology in adipocytes, ameliorating the pathology in muscle cells, and

type II diabetes; a broad range of oncology indications, including blocking the migration, invasion and metastasis in many different tumor types; and T-cell mediated autoimmune diseases.

V. Organic Synthetic Techniques

[0095] A wide array of organic synthetic techniques exist in the art to meet the challenge of constructing 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 suh 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.

VI. Alternative Compound Forms or Derivatives

[0096] Alternative forms or derivatives, such as (a) Isomers, Prodrugs, and Active Metabolites (b) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms (c) Prodrugs and Metabolites (d) Pharmaceutically acceptable salts and (e) Polymorphic forms, are described, for example, in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety.

VII. Administration

[0097] 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. In this context, the terms "subject," "animal subject," and the like refer to human and non-human vertebrates, e.g. mammals, such as non-human primates, sports and commercial animals, e.g., equines, bovines, porcines, ovines, rodents, and pets, e.g., canines and felines. A description of possible methods and routes of administration may be found, for example, in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety.

EXAMPLES

[0098] A number of examples illustrative of the present invention are described below. In most cases, alternative techniques could also be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. Unless specifically noted to the contrary, in cases where a compound number is not preceeded by a "P-" (e.g., "P-0001") in the Examples section, compound naming and/or enumeration is not related to naming and/or enumeration employed in other sections of this application. Similarly, structure and substituent

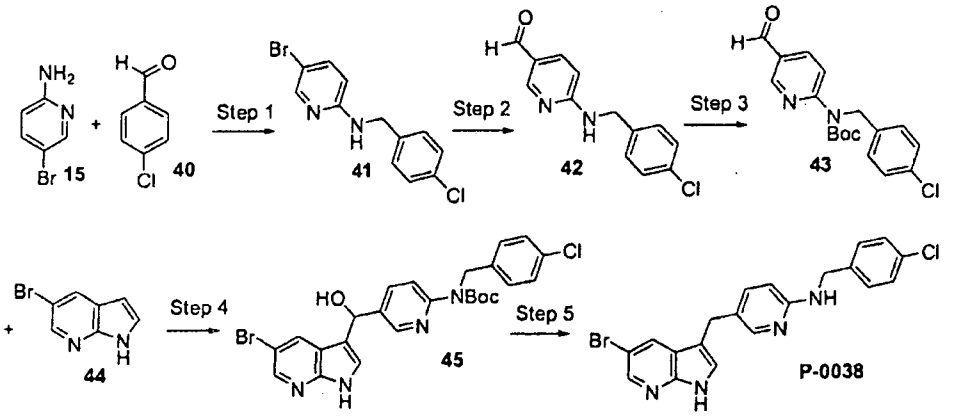
naming and enumeration within the Examples are independent of structure and substituent naming and enumeration in above sections of this application unless clearly indicated otherwise.

[0099] In the following Examples, it is understood that the solvents and reagents used or suggested are not limiting, and can be substituted appropriately with solvents and reagents known to those of skill in the art. Reaction products may be isolated by means known in the art, such as extraction with a suitable solvent, precipitation from a suitable solvent, chromatography using a suitable solvent system, including silica gel column chromatography, HPLC, preparative TLC, and the like. Exemplary methods for synthesis of compounds of the present invention may be found in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference. The 1H-pyrrolo[2,3-b]pyridine core of compounds described in the examples may also be referred to as 7-azaindole in the examples.

Example 1: Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (P-0038)

[0100] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine **P-0038** was synthesized in 5 steps from commercially available 2-Amino-5-bromopyridine **15** as shown in Scheme 19.

Scheme 19



Step 1- Synthesis of (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine **(41)**

[0101] To 2-Amino-5-bromopyridine (**15**, 6.10 g, 0.0352 mol) in toluene (90.0 mL) were added 4-chlorobenzaldehyde (**40**, 5.00 g, 0.0356 mol), trifluoroacetic acid (8.0 mL, 0.10 mol) and triethylsilane (16.5 mL, 0.103 mol). The reaction was heated to reflux for 48 hours. The reaction

was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude residue was crystallized with ethyl acetate to give compound (**41**, 6.8 g, 65.4%).

Step 2 – Synthesis of 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (**42**)

[0102] To (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine (**41**, 10.00 g, 0.03360 mol) in tetrahydrofuran (400.0 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (17.5 mL, 2.00 M in cyclohexane). After 90 minutes, tert-butyllithium (42.00 mL, 1.70 M in hexane) was added to the reaction. After 80 minutes, N,N-dimethylformamide (6.9 mL, 0.089 mol) was added to the reaction. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give the crude compound, which was crystallized from *tert*-butoxyl methyl ether to provide compound (**42**, 7.66 g, 92.2%).

Step 3 – Synthesis of (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**43**)

[0103] To 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (**42**, 2.00 g, 8.11 mmol) in dichloromethane (20.0 mL) were added triethylamine (1.70 mL, 12.2 mmol), di-tert-butyldicarbonate (2.00 g, 9.16 mmol) and 4-dimethylaminopyridine (52.3 mg, 0.43 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give compound (**43**, 2.50 g, 89.3%).

Step 4 – Synthesis of {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**45**)

[0104] To 5-bromo-7-azaindole (**44**, 198.0 mg, 1.01 mmol) in methanol (30.0 mL, 0.741 mol) were added (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**43**, 355.0 mg, 1.02 mmol) and potassium hydroxide (80.0 mg, 1.42 mmol). The reaction was stirred at room temperature 48 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 8% methanol in dichloromethane to give compound (**45**, 200.0 mg, 36.8%).

Step 5 – Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (**P-0038**)

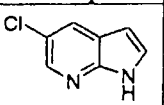
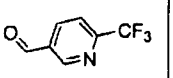
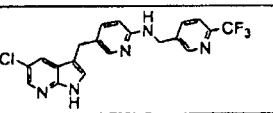
[0105] To {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**45**, 180.0 mg, 0.33 mmol) in acetonitrile (30.0 mL) were added trifluoroacetic acid (2.0 mL, 0.026 mol) and triethylsilane (4.0 mL, 0.025 mol). The reaction was heated to reflux for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0038**, 120 mg, 85.2%). MS(ESI)$[M+H^+]^+$ = 427.2, 429.2.

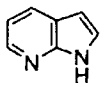
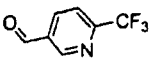
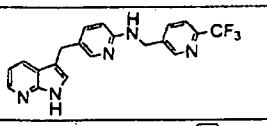
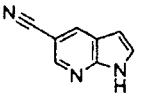
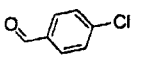
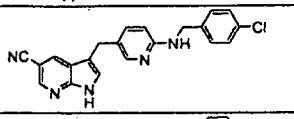
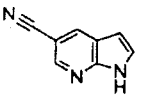
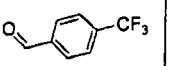
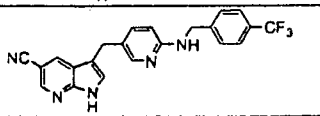
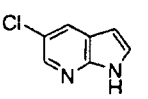
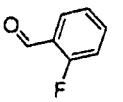
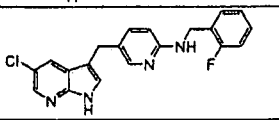
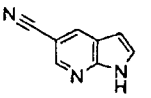
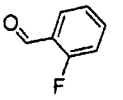
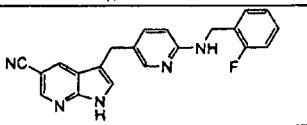
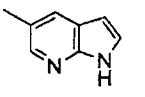
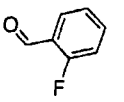
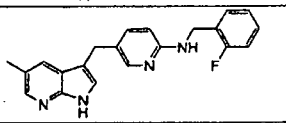
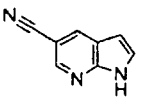
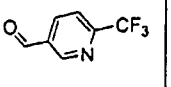
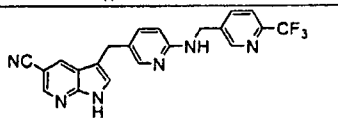
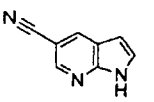
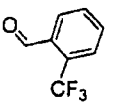
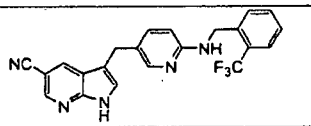
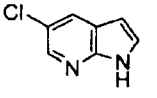
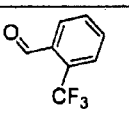
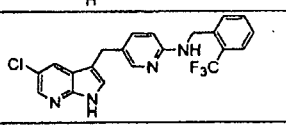
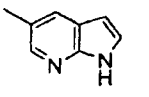
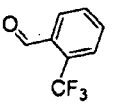
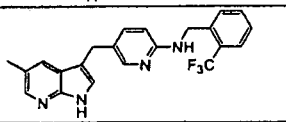
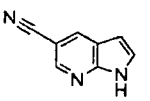
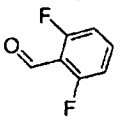
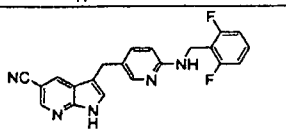
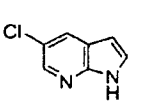
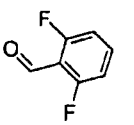
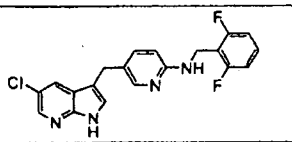
[0106] Additional compounds were prepared following the protocol of Scheme 19, optionally replacing 4-chlorobenzaldehyde **40** with an appropriate aldehyde in Step 1 and optionally replacing 5-bromo-7-azaindole **44** with an appropriate azaindole in Step 4. The following compounds were made following this procedure:
[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**),
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0257**),
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0269**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine (**P-0270**),
3-[6-(2-Fluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0271**),
(2-Fluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0272**),
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0273**),
3-[6-(2-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0274**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0275**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-

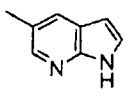
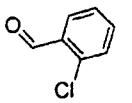
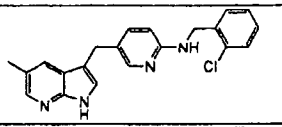
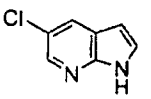
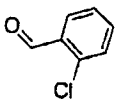
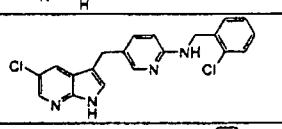
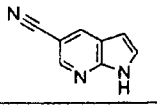
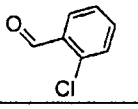
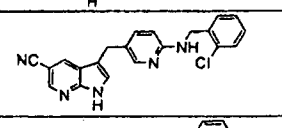
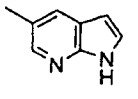
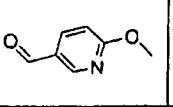
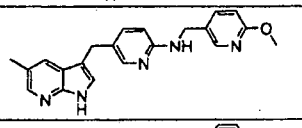
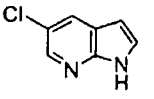
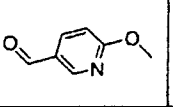
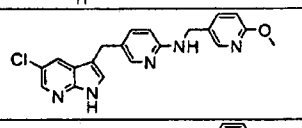
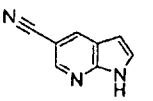
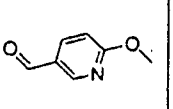
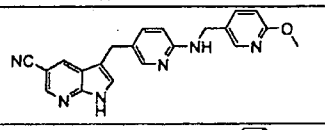
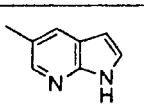
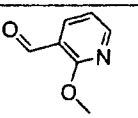
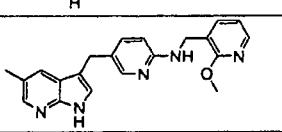
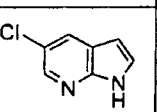
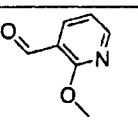
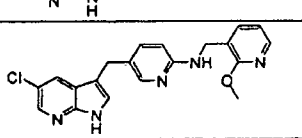
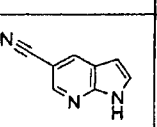
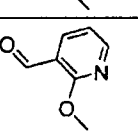
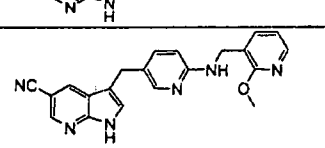
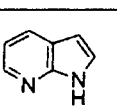
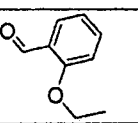
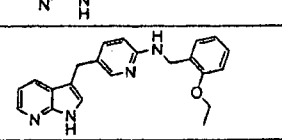
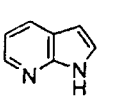
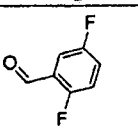
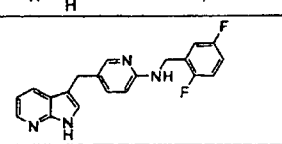
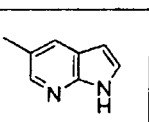
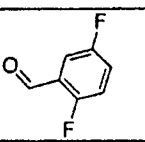
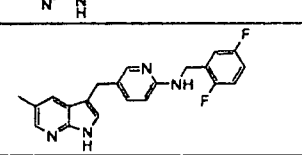
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3-[6-(2,6-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0277**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine (**P-0278**),
(2-Chloro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0279**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0280**),
3-[6-(2-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0281**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0282**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0283**),
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**),
(2-Ethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0288**),
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0296**),
(2,5-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0297**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,5-difluoro-benzyl)-amine (**P-0298**),
3-[6-(2,5-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0299**),
3-[6-(2-Trifluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0321**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0322**),
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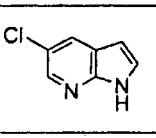
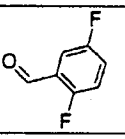
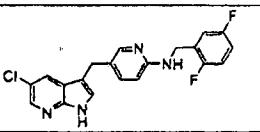
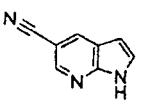
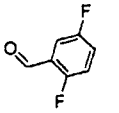
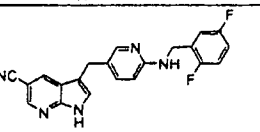
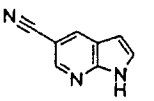
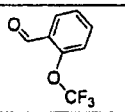
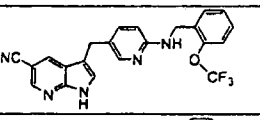
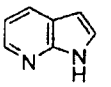
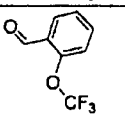
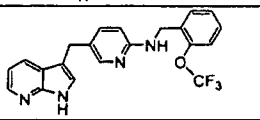
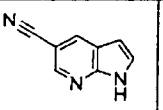
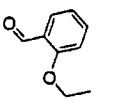
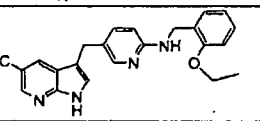
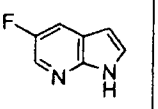
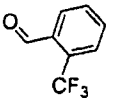
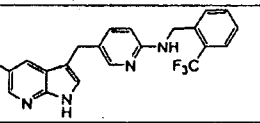
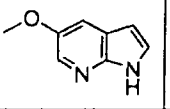
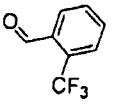
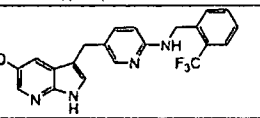
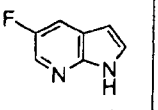
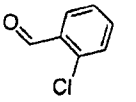
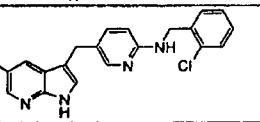
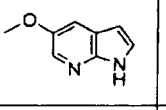
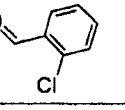
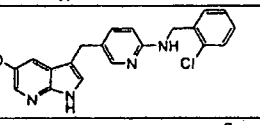
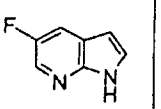
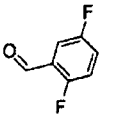
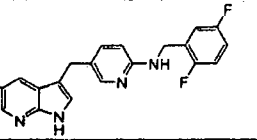
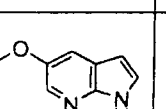
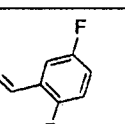
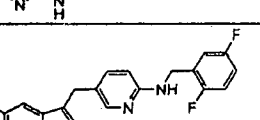
(**P-0323**),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0325**),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0326**),
(2-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0327**),
(2-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0328**),
(2,5-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0329**),
(2,5-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0330**),
[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**),
(2,6-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0333**),
(2,6-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0334**),
(2-Methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0336**),
3-[6-(2-Methoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0337**),
(2,6-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0340**), and
(2,6-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0341**).

The following table indicates the aldehyde used in Step 1 in Column 3 and the azaindole used in Step 4 in Column 2 to provide the compound of Column 4. Column 1 provides the compound number and Column 5 the measured mass spectrometry result.

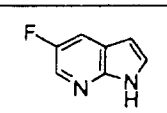
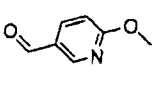
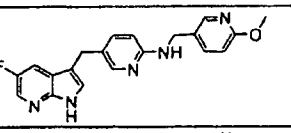
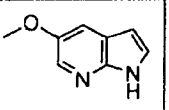
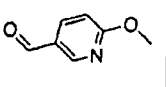
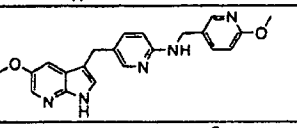
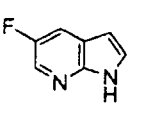
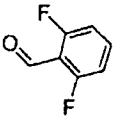
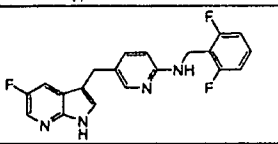
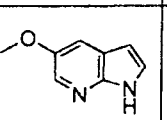
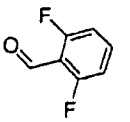
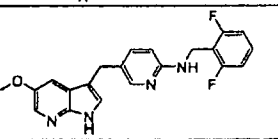
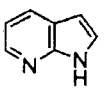
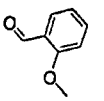
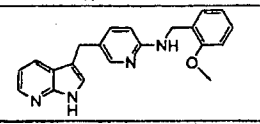
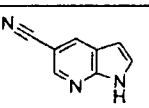
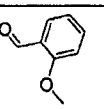
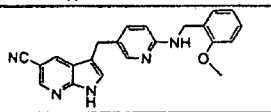
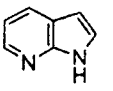
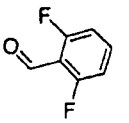
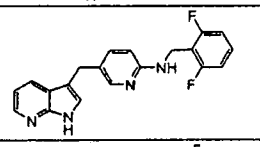
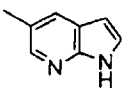
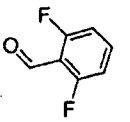
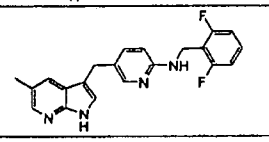
Compound number	Azaindole in Step 4	Aldehyde in Step 1	Compound structure	MS $[M+H^+]^+$
P-0181				418.2

P-0182				384.2
P-0257				374.2
P-0269				408.7
P-0270				367.0
P-0271				358.0
P-0272				347.0
P-0273				409.4
P-0274				408.5
P-0275				417.0
P-0276				397.6
P-0277				376.5
P-0278				385.0

P-0279				363.0
P-0280				383.3
P-0281				374.0
P-0282				360.8
P-0283				380.0
P-0284				371.5
P-0285				360.1
P-0286				380.0
P-0287				371.0
P-0288				359.6
P-0296				351.6
P-0297				365.5

P-0298				385.9
P-0299				376.4
P-0321				424.6
P-0322				399.5
P-0323				384.7
P-0325				401.5
P-0326				413.4
P-0327				367.2
P-0328				379.0
P-0329				369.7
P-0330				381.6

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P-0331				364.5
P-0332				376.4
P-0333				369.6
P-0334				381.6
P-0336				345.7
P-0337				370.7
P-0340				351.5
P-0341				365.5

[0107] Additional compounds were prepared following the protocol of Scheme 19, Steps 4 and 5, replacing (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **43** with an appropriate protected aldehyde and 5-bromo-7-azaindole **44** with an appropriate azaindole in Step 4. Aldehydes were prepared as described in Example 60. The following compounds were made following this procedure:

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**),

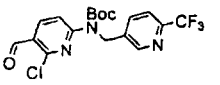
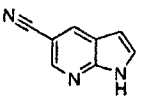
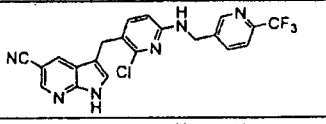
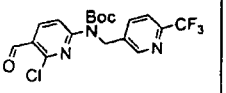
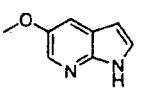
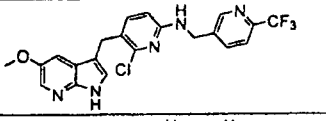
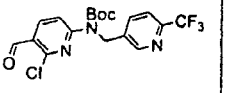
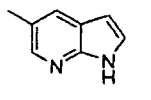
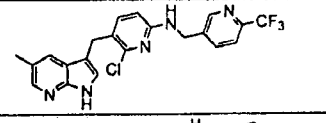
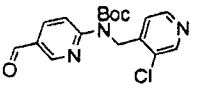
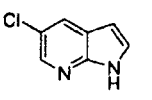
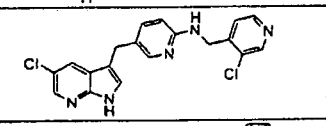
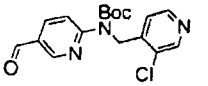
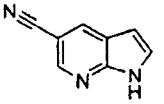
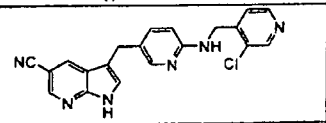
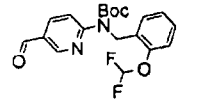
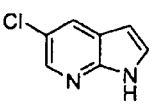
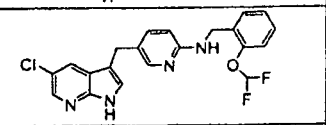
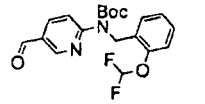
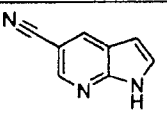
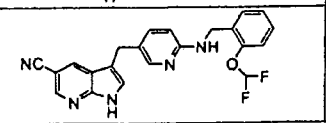
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0235**),

3-{6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0256**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-difluoromethoxy-benzyl)-amine (**P-0338**),

3-[6-(2-Difluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0339**),

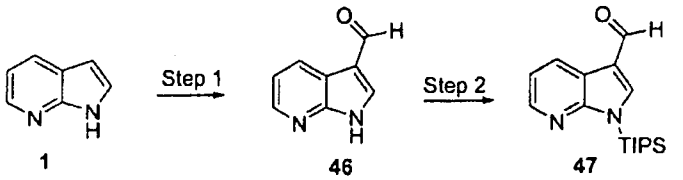
The following table indicates the aldehyde used in Column 2 and the azaindole used in Column 3 to provide the compound of Column 4. Column 1 provides the compound number and Column 5 the measured mass spectrometry result.

Compound number	Aldehyde	Azaindole	Compound	MS $[M+H^+]^+$
P-0232				443.0
P-0233				$[M-H^+]^-$ = 446.1
P-0234				430.1
P-0235				383.9
P-0256				375.2
P-0338				415.0
P-0339				406.6

Example 2: Synthesis of 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde 47.

[0108] Compound **47** was synthesized in 2 steps from 7-azaindole **1** as described in Scheme 20.

Scheme 20



1 46 47

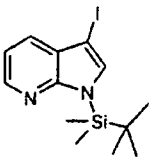
Step 1 – *Preparation of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde* (**46**):

[0109] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 16.0 g, 135 mmol) in water (110 mL), were added hexamethylenetetramine (26.0 g, 185 mmol), and acetic acid (55.0 mL, 967 mmol). The reaction was refluxed for 12 hours. Water (329 mL) was added and the reaction was cooled to room temperature. The reaction was filtrated and washed with water to give compound (**46**, 15.0 g, 76%). MS(ESI)$[M+H^+]^+ = 147$.

Step 2 – *Preparation of 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde* (**47**):

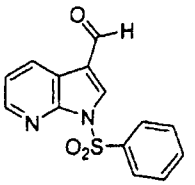
[0110] To 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde (**46**, 4.05 g, 27.71 mmol) in tetrahydrofuran (30.0 mL) were added sodium hydride (60% in mineral oil, 1.5 g, 38 mmol) and triisopropylsilyl chloride (8.0 mL, 38 mmol) under an atmosphere of nitrogen. The reaction was stirred for 2 hours at room temperature. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 10 % ethyl acetate in hexane to give compound (**47**, 3.0 g, 36%). MS(ESI)$[M+H^+]^+ = 303$.

[0111] 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine **66**



was prepared following the protocol of Scheme 20 Step 2, substituting 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde **46** with 3-iodo-1H-pyrrolo[2,3-b]pyridine and triisopropylsilyl chloride with tert-Butyl-dimethyl-silyl chloride.

[0112] 1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **55**

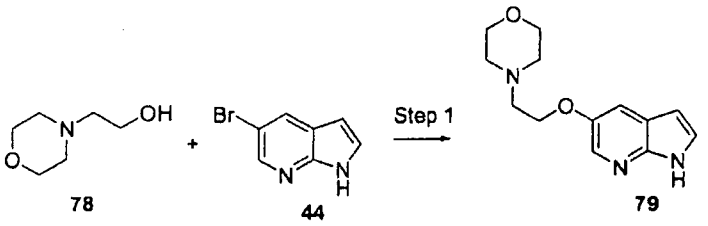


was prepared following the protocol of Scheme 20, substituting triisopropylsilyl chloride with benzenesulfonyl chloride in Step 2.

Example 3: Synthesis of 5 substituted 7-azaindole intermediates

[0113] 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine **79** was synthesized in 1 Step from commercially available 5-bromo-azaindole as shown in Scheme 31.

Scheme 31



Step 1 – 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine (**79**):

[0114] To 4-morpholineethanol (30 mL, 0.2 mol) in N, N-dimethylformamide (30 mL) was slowly added sodium hydride (7 g, 60% dispersion in mineral oil, 0.2 mol). After the solution turned clear, a solution of 5-bromo-7-azaindole (**44**, 1.0 g, 0.0051 mol) in N,N-dimethylformamide (5 mL) and copper(I) bromide (1.4 g, 0.0098 mol) were added. The reaction mixture was stirred at 120 °C under nitrogen for 2 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected, washed with a solution of ammonium chloride and ammonium hydroxide (4:1), brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**79**, 0.62 g, 50%). MS (ESI) $[M+H^+]^+ = 248.25$.

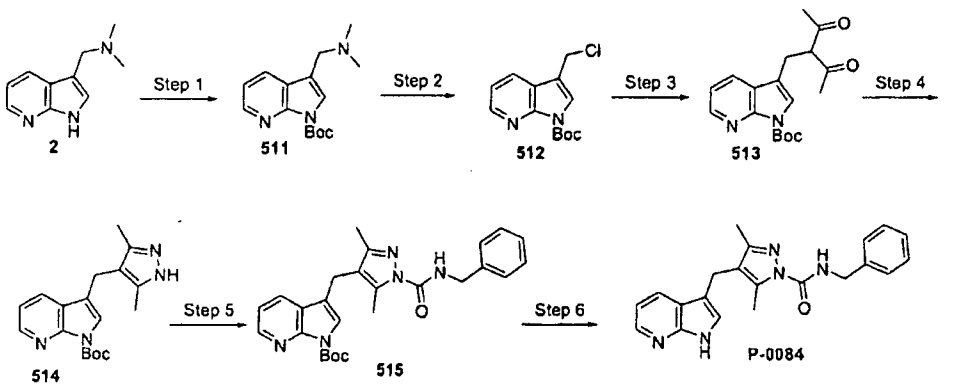
[0115] Additional 5-substituted 7-azaindoles were prepared following the protocol of Scheme 31, replacing 4-morpholineethanol with either 2-diethylamino-ethanol, 3-diethylamino-propan-1-ol, 2-piperidin-1-yl-ethanol, or 2-pyrrolidin-1-yl-ethanol to provide diethyl-[2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)-ethyl]-amine, Diethyl-[3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-propyl]-amine, 5-(2-piperidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, and 5-(2-pyrrolidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, respectively.

Example 4: Synthesis of 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084

[0116] 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084 was synthesized in 6 steps from dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** as shown in Scheme 158.

Scheme – 158



Step 1: Preparation of 3-Dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (511)

[0117] To dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine (**2**, 2.50 g, 14.3 mmol,) in tetrahydrofuran (200.0 mL) was added sodium hydride (0.685 g, 60% in mineral oil, 17.1 mmol). After 10 minutes, di-*tert*-butyldicarbonate (3.74 g, 17.1 mmol) was added to the reaction. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give as a white solid (**511**, 3.80 g, 96.7%).

Step 2: Preparation of 3-Chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (512)

[0118] To 3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**511**, 2.60 g, 9.44 mmol) in toluene (50.00 mL) was added isopropyl chloroformate (11.3 mL, 1.0 M in toluene) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3

hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**512**, 2.0 g, 79.4%).

Step 3 – Preparation of 3-(2-Acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (513):

[0119] To acetylacetone (0.563 g, 5.62 mmol) in dimethyl sulfoxide (29.0 mL) was added sodium hydride (0.225 g, 60% in mineral oil, 5.62 mmol). After 20 minutes, 3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**512**, 1.00 g, 3.75 mmol) was added to the reaction. The reaction was stirred at room temperature for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 40% ethyl acetate in hexane to give a colorless oil (**513**, 0.59 g, 48.0%). MS (ESI) $[M+H^+]^+ = 331.4$.

Step 4 – Preparation of 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (514)

[0120] To 3-(2-acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**513**, 1.20 g, 3.63 mmol) in methanol (15.0 mL), cooled to -20 °C under an atmosphere of nitrogen, was added hydrazine (0.128 g, 4.00 mmol) in dichloromethane (6.0 mL). The reaction was stirred for 2 hours. The reaction was concentrated to remove the solvents, and the residue was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 60% ethyl acetate in hexane to give a white solid (**514**, 1.0 g, 84.4%). MS (ESI) $[M+H^+]^+ = 327.4$.

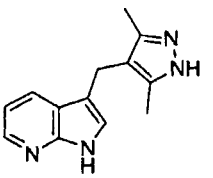
Step 5 – Preparation of 3-(1-Benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (515)

[0121] To 3-(3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 60.0 mg, 0.18 mmol) in dichloromethane (6.0 mL) were added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.033 mL, 0.220 mmol) and benzyl isocyanate (29.4 mg, 0.220 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 2 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give crude compound (**515**, approx. 50 mg) that was used in the next step directly. MS (ESI) $[M+H^+]^+ = 460.5$.

Step 6 - 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide (P-0084)

[0122] To 3-(1-benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**515**, 50.0 mg, 0.11 mmol) in dichloromethane (6.0 mL) was added trifluoroacetic acid (0.20 mL, 2.6 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 20 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**P-0084**, 11.0 mg, 28.1%). MS (ESI) $[M+H^+]^+ = 360.5$.

[0123] 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine **P-0124**



was prepared from 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 15.0 mg, 0.046 mmol) by dissolving in dichloromethane (10.0 mL) to which trifluoroacetic acid (0.10 mL, 1.3 mmol) was added. The reaction was stirred at room temperature for 1 hour, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate in hexane to give an off-white solid (**P-0124**, 7.5 mg, 72.0%). MS (ESI) $[M+H^+]^+ = 227.3$.

[0124] Additional compounds were prepared following the protocol of Scheme 158, replacing dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** with (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (prepared as described in Example 10, Scheme 164, isolated after step 1) in Step 1 and replacing benzyl isocyanate with an appropriate electrophile in Step 5. The following compounds were made following this procedure:

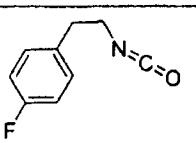
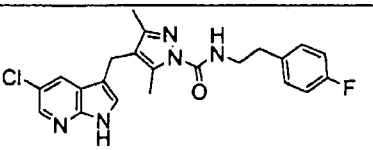
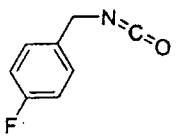
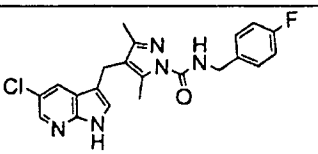
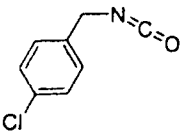
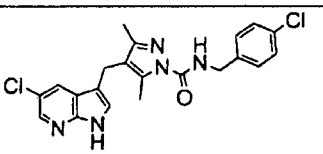
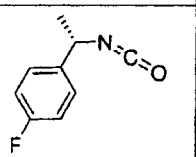
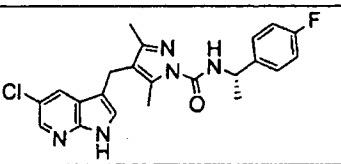
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide (**P-0157**),

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-fluoro-benzylamide (**P-0158**),

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-chloro-benzylamide (**P-0159**), and

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [(S)-1-(4-fluoro-phenyl)-ethyl]-amide (**P-0160**).

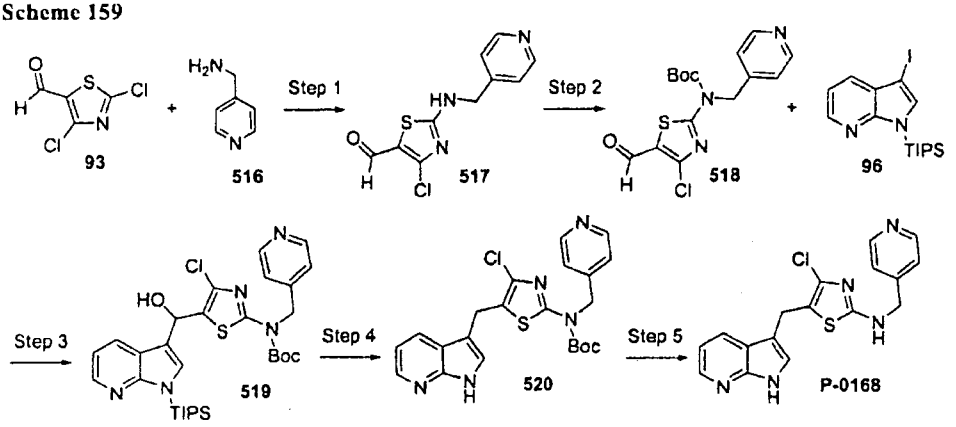
[0125] The electrophile used in place of benzyl isocyanate in Step 5 is indicated in Column 2 of the following table, with the compound structure given in Column 3. Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

	Electrophile	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0157			426.2
P-0158			412.2
P-0159			428.2
P-0160			426.2

Example 5: Synthesis of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine P-0168

[0126] [4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine **P-0168** was synthesized in 5 steps as shown in Scheme 159.

Scheme 159



Step 1 – Preparation of 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (517):

[0127] To a solution of 4-(aminomethyl)pyridine (**516**, 1.16 mL, 11.5 mmol) and N,N-diisopropylethylamine (3.8 mL, 22 mmol) in tetrahydrofuran (50 mL) was added 2,4-dichloro-thiazole-5-carbaldehyde (**93**, 2.0 g, 11.0 mmol) in tetrahydrofuran (5 mL) 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, and dried over sodium sulfate. The crude compound 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (**517**) was used for the next step without purification.

Step 2 – Preparation of (4-chloro-5-formyl-thiazol-2-yl)-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (518):

[0128] A mixture of 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (**517**, 3.28 g, 11.0 mmol), di-tert-butyldicarbonate (4.0 g, 18 mol) and triethylamine (10 mL, 74 mmol) in dichloromethane (120 mL) was stirred at room temperature for 6 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**518**, 564 mg, 15%). MS (ESI) $[M+H^+]^+ = 354.1$.

Step 3 – Preparation of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (519):

[0129] To a solution of 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.44 g, 1.1 mmol) in tetrahydrofuran (20 mL) at -20 °C, isopropylmagnesium chloride (2 M in tetrahydrofuran, 0.6 mL, 1.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C in 10 minutes. The reaction mixture was then cooled to -40 °C. A solution of (4-

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chloro-5-formyl-thiazol-2-yl)-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**518**, 0.26 g, 0.73 mmol) in tetrahydrofuran (4 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to -10 °C over 30 minutes. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**519**, 397 mg, 86%). MS (ESI) $[M+H^+]^+ = 628.3$.

Step 4 – Preparation of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (520):

[0130] A mixture of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**519**, 0.397 g, 0.57 mmol), triethylsilane (1.0 mL, 6.3 mmol), and trifluoroacetic acid (0.5 mL, 6 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**520**, 126 mg, 49%). MS (ESI) $[M+H^+]^+ = 456.2$.

*Step 5 – Preparation of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine (**P-0168**):*

[0131] To a solution of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**520**, 126 mg, 0.000276 mol) in dichloromethane (2 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into cold sodium bicarbonate solution, extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After removal of solvents, the residue was washed with ethyl acetate to provide the desired compound as a light yellow solid (**P-0168**, 68.4 mg, 70%). MS (ESI) $[M+H^+]^+ = 356.2$.

[0132] Additional compounds were prepared following the protocol of Scheme 159, replacing 4-(aminomethyl)pyridine **516** with an appropriate amine. The following compounds were made following this procedure:

[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]-pyridin-2-ylmethyl-amine (**P-0167**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine (**P-0171**),

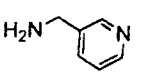
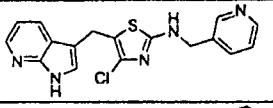
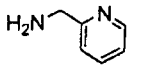
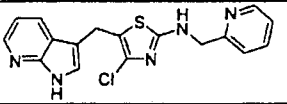
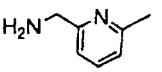
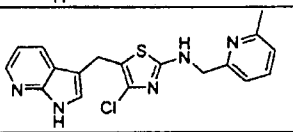
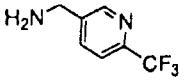
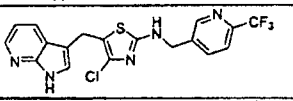
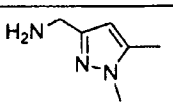
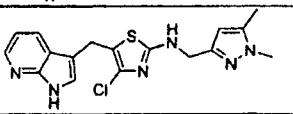
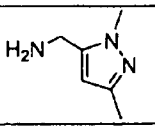
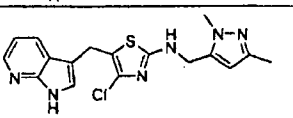
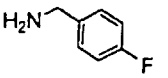
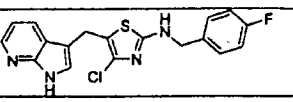
[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0173**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amine (**P-0172**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amine (**P-0175**), and

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0156**).

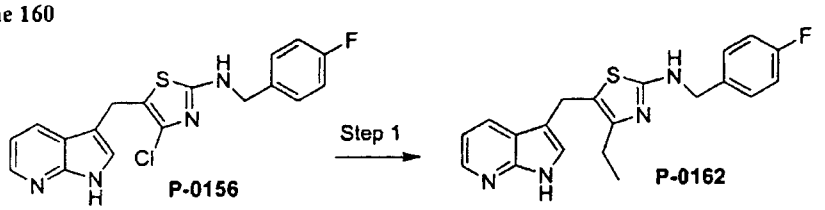
The following table indicates the amine (Column 2) used in Scheme 159 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0164			356.1
P-0167			356.1
P-0171			370.2
P-0173			424.2
P-0172			373.2
P-0175			373.2
P-0156			373.1

Example 6: Synthesis of [4-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine P-0162 and (4-fluoro-benzyl)-[4-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine P-0162

[0133] [4-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0162** was synthesized in 1 step from [4-chloro-5-(1H-pyrrolo[2, 3-b] pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0156** as shown in Scheme 160.

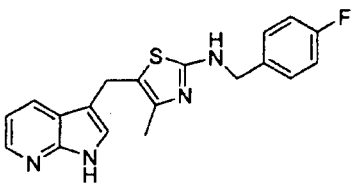
Scheme 160



Step 1 – Preparation of [4-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (P-0162):

[0134] Into a round bottom flask, under an atmosphere of nitrogen, [1,1'-bis(diphenyl phosphino) ferrocene] dichloro palladium (II), complex with dichloromethane (1:1), was placed with toluene (15 mL, 140 mmol). [4-Chloro-5-(1H-pyrrolo[2,3-b] pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0156**,145 mg, 0.4 mmol) was added in 5 ml of toluene at room temperature. The mixture was stirred for 10 minutes. To the stirring reaction, a solution of 3.13 M ethyl magnesium bromide in ether (1.86 mL) was added dropwise at room temperature. The opaque solution was heated to 60 °C. Tetrahydrofuran (10 mL) was added to the warm solution. The mixture was heated to reflux for an additional two hours. After cooling to 0 °C, the reaction was quenched with a solution of citric acid at pH 4-5 in ice-water and stirred to room temperature. The mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Purification with flash chromatography, eluting with a gradient of ethyl acetate:hexanes (20:100), gave a yellow solid that was further washed with ethyl acetate to give P-0162 (15 mg,10%) as an off-white solid. MS (ESI) $[M+H^+]^+ = 367.2$.

[0135] (4-Fluoro-benzyl)-[4-methyl-5-(1H-p yrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **P-0163**

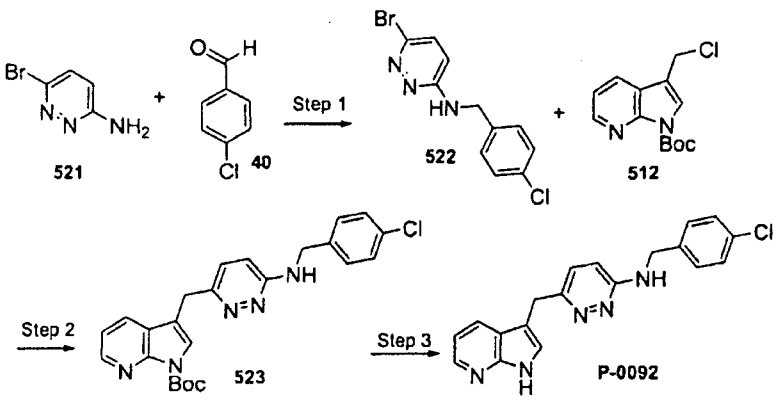


was prepared using the protocol of Scheme 160, substituting the 3.13 M ethyl magnesium bromide in ether solution with 1.4 M of methylmagnesium bromide in tetrahydrofuran. MS (ESI) $[M+H^+]^+$ = 353.2.

Example 7: Synthesis of (4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine P-0092

[0136] (4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine **P-0092** was synthesized in 3 steps as shown in Scheme 161.

Scheme 161



Step 1 – Synthesis of (6-bromo-pyridazin-3-yl)-(4-chloro-benzyl)-amine (522):

[0137] To 6-bromo-pyridazin-3-ylamine (**521**, 0.85 g, 0.0049 mol) in acetonitrile (30.0 mL) were added 4-chlorobenzaldehyde (**40**, 0.82 g, 0.0058 mol), triethylsilane (4.0 mL, 0.025 mol) and trifluoroacetic acid (2.0 mL, 0.026 mol). The reaction was heated to reflux for 4 hours, then poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and washed with ethyl acetate to give a white solid (**522**, 1.0 g). MS (ESI) $[M+H^+]^+$ = 298.3, 300.2.

Step 2 – Preparation of 3-[6-(4-chloro-benzylamino)-pyridazin-3-ylmethyl]-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (523):

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[0138] To (6-bromo-pyridazin-3-yl)-(4-chloro-benzyl)-amine (**522**, 0.560 g, 1.88 mmol) in tetrahydrofuran (45.0 mL), under an atmosphere of nitrogen at -78 °C, was added n-butyllithium (2.50 M in hexane, 0.760 mL) slowly. After 10 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (0.201 g, 0.94 mmol) in tetrahydrofuran (5.0 mL) was added to the reaction. The reaction mixture was allowed to stir at room temperature for 3 hours. The reaction was cooled to -78 °C, followed by addition of 1.70 M of tert-butyllithium in hexane (1.20 mL) slowly. The reaction was stirred for 20 minutes, followed by addition of a solution of CuCN.2LiCl (0.6 M in tetrahydrofuran, 3.00 mL) and 3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**512**, 0.47 g, 1.8 mol) in tetrahydrofuran (10.0 mL). After 30 minutes, the reaction was allowed to warm to room temperature for 10 minutes. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was treated with trifluoroacetic acid (1.0 mL) dissolved in dichloromethane (10.0 mL) for 10 minutes. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified with silica gel column chromatography eluting with 60% ethyl acetate in hexane to give the desired compound (**523**, 0.10 g, 23.8%). MS (ESI) $[M+H^+]^+ = 450.1$.

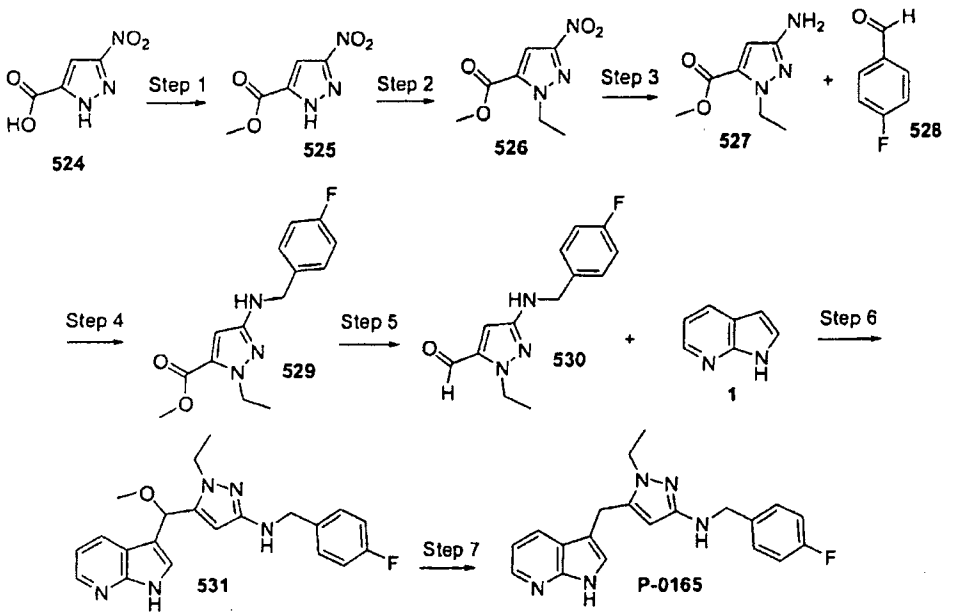
Step 3 – Preparation of (4-chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine (P-0092):

[0139] To 3-[6-(4-chloro-benzylamino)-pyridazin-3-ylmethyl]-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**523**, 50.0 mg, 0.111 mmol) in dichloromethane (10.0 mL) was added trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at room temperature overnight. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give an off-white solid (**P-0092**, 7.3 mg, 19.0%). MS (ESI) $[M+H^+]^+ = 350.1$.

Example 8: Synthesis of [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine P-0165

[0140] [1-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0165** was synthesized in 7 steps as shown in Scheme 162.

Scheme 162



Step 1 – Preparation of 5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (525):

[0141] To 5-nitro-2H-pyrazole-3-carboxylic acid (**524**, 10.0 g, 0.0637 mol) in methanol (100.0 mL) was added concentrated sulfuric acid (1.00 mL, 0.0180 mol). The reaction was stirred at room temperature overnight. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**525**, 1.5 g, 13.8%).

Step 2 – Preparation of 2-ethyl-5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (526):

[0142] To 5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (**525**, 2.50 g, 0.0146 mol) in N,N-dimethylformamide (62.5 mL) were added iodoethane (1.2 mL, 0.016 mol) and potassium carbonate (4.17 g, 0.0301 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**526**, 1.3 g, 44.7%).

Step 3 – Preparation of 5-amino-2-ethyl-2H-pyrazole-3-carboxylic acid methyl ester (527):

[0143] To 2-ethyl-5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (**526**, 1.30 g, 6.53 mmol) in methanol (60.0 mL) was added 20% $Pd(OH)_2/C$ (0.1 g). The reaction was stirred under an atmosphere of hydrogen overnight. The reaction was filtered and concentrated to give a light yellow solid (**527**, 1.0 g, 90.6%).

Step 4 – Preparation of 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carboxylic acid methyl ester (529):

[0144] To 5-amino-2-ethyl-2H-pyrazole-3-carboxylic acid methyl ester (**527**, 1.00 g, 5.91 mmol) in acetonitrile (27.5 mL) were added 4-fluorobenzaldehyde (**528**, 0.660 mL, 6.26 mmol), triethylsilane (4.77 mL, 0.0298 mol) and trifluoroacetic acid (2.38 mL, 0.0310 mol). The reaction was stirred at 80 °C for 4 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**529**, 1.00 g, 61%).

Step 5 – Preparation of 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (530):

[0145] To 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carboxylic acid methyl ester (**529**, 1.00 g, 3.61 mol) in tetrahydrofuran (70.0 mL) under an atmosphere of nitrogen at room temperature, lithium tetrahydroaluminate (1.00 M of in tetrahydrofuran, 10.00 mL) was slowly added. The reaction was stirred at room temperature overnight, followed by slowly adding sodium sulfate decahydrate (15.0 g). After 2 hours, the reaction was filtered, concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow oil (**530**, 0.16 g, 18%). MS (ESI) $[M+H^+]^+ = 248.2$.

Step 6 – Preparation of 1-ethyl-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-1H-pyrazol-3-yl-(4-fluoro-benzyl)-amine (531):

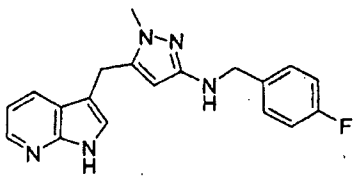
[0146] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 54.0 mg, 0.46 mmol) in methanol (15.0 mL) were added 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 110.0 mg, 0.44 mmol) and potassium hydroxide (0.60 g, 0.011 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 40% ethyl acetate in hexane to give a white solid (**531**, 0.12 g, 71.1%). MS (ESI) $[M-H^+]^- = 378.2$.

*Step 7 – Preparation of [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-0165**):*

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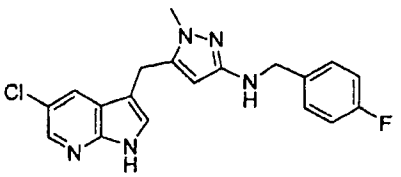
[0147] To 1-ethyl-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-1H-pyrazol-3-yl-(4-fluoro-benzyl)-amine (**531**, 0.12 g, 0.32 mmol) in acetonitrile (10.0 mL, 0.191 mol) were added triethylsilane (0.60 mL, 0.0038 mol) and trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at 80 °C for 2 hours. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give crude compound. ^{1}H NMR indicated that the reaction was incomplete. The crude compound was dissolved in dichloromethane (15.0 mL), trifluoroacetic acid (0.30 mL) and triethylsilane (0.60 mL). The reaction was stirred at 43 °C for 72 hours. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give an off-white solid (**P-0165**, 18.7 mg, 17%). MS (ESI) $[M+H^+]^+$ = 350.3.

[0148] (4-Fluoro-benzyl)-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-amine **P-0169**



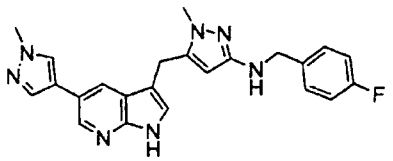
was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in Step 2. MS (ESI) $[M+H^+]^+$ = 336.3.

[0149] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0170**



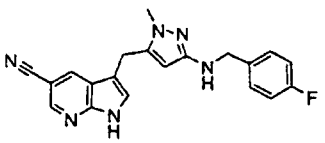
was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in step 2 and 1H-pyrrolo[2,3-b]pyridine **1** with 5-chloro-1H-pyrrolo[2,3-b]pyridine in step 6. MS (ESI) $[M+H^+]^+$ = 370.3

[0150] (4-Fluoro-benzyl)-{1-methyl-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-1H-pyrazol-3-yl}-amine **P-0180**



was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in step 2 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (prepared as described in Example 18, Scheme 172) in step 6. MS (ESI) $[M+H^+]^+ = 416.2$.

[0151] 3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0191**

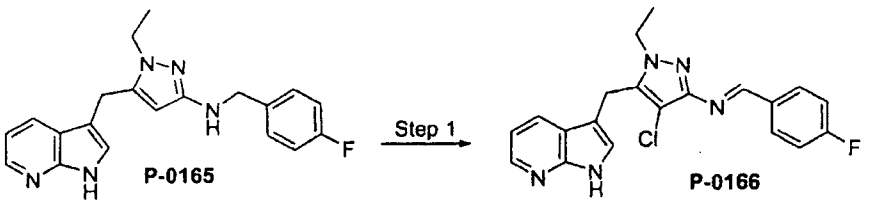


was prepared using the protocol of Scheme 162, substituting 1H-Pyrrolo[2,3-b]pyridine **1** with 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile in Step 6. MS (ESI) $[M+H^+]^+ = 361.5$.

Example 9: Synthesis of [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine P-0166

[0152] [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine **P-0166** was synthesized in 1 step as shown in Scheme 163.

Scheme 163



Step 1 – Preparation of [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine (P-0166):

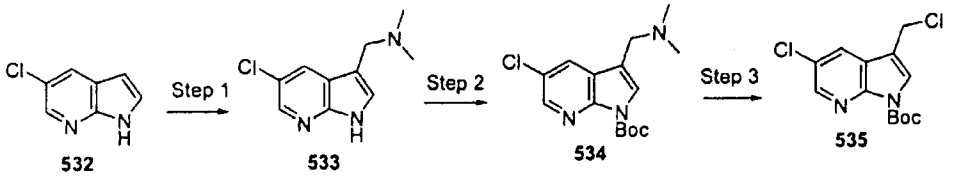
[0153] To [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-0165**, 10.1 mg, 0.0289 mmol, prepared as described in Example 8, Scheme 162) in acetonitrile (8.0 mL) was added N-chloro-succinimide (4.18 mg, 0.0318 mmol). The reaction was stirred at room temperature for 2 hours. The reaction was concentrated and purified by silica gel

column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (P-0166, 1.1 mg). MS (ESI) $[M+H^+]^+ = 382.1$.

Example 10: Synthesis of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester

[0154] 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester was synthesized in 3 steps as shown in Scheme 164.

Scheme 164



Step 1 – Preparation of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (533):

[0155] To 5-Chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 8.00 g, 0.0524 mol) in isopropyl alcohol (250.0 mL) were added dimethylamine hydrochloride (4.79 g, 0.0587 mol) and formaldehyde (1.77 g, 0.0589 mol). 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 (**533**, 10.0 g, 91%), that was used directly in the next step.

Step 2 and 3 – Preparation of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (535):

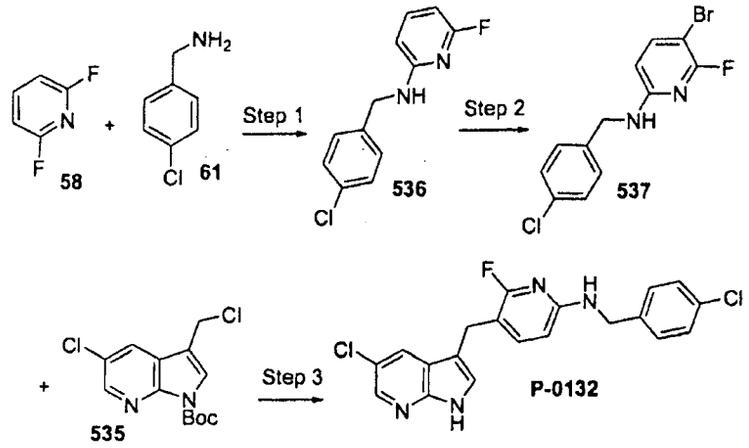
[0156] 5-Chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester **535** was prepared following the protocol of Scheme 158 (Example 4) steps 1 and 2, substituting dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** with (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine **533** in step 1.

Example 11: Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine P-0132

[0157] (4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **P-0132** was synthesized in 3 steps as shown in Scheme 165.

Scheme 165

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Step 1 – Preparation of (4-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (536):

[0158] To 2,6-difluoropyridine (**58**, 9.85 g, 0.0856 mol) in N-methylpyrrolidinone (50.0 mL) were added p-chlorobenzylamine (**61**, 10.5 mL, 8.63 mmol) and N,N-diisopropylethylamine (30.0 mL, 0.172 mol). The reaction was stirred at 90 °C overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25% ethyl acetate in hexane, then washed with ethyl acetate/hexane to give a white solid (**536**, 10 g, 50%).

Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-amine (537):

[0159] To (4-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (**536**, 1.03 g, 4.35 mmol) in acetonitrile (30.0 mL), under an atmosphere of nitrogen, N-bromosuccinimide (0.820 g, 4.61 mol) was added slowly. After 2 hours, the reaction was poured into a solution of sodium thiosulfate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and crytstallized with ethyl acetate and hexane to give a white solid (**537**, 1.10 g, 80.1%).

Step 3 – Preparation of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (P-0132):

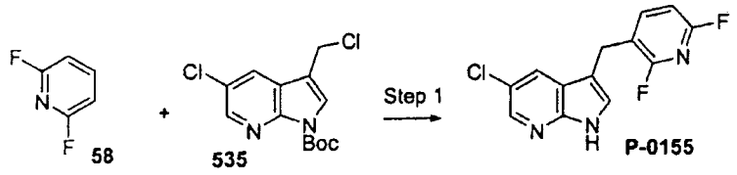
[0160] To (5-bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-amine (**537**, 2.76 g, 8.75 mol) in tetrahydrofuran (90.0 mL), under an atmosphere of nitrogen at -78 °C, n-butyllithium (2.50 M in hexane, 3.64 mL) was added slowly. After 60 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (0.942 g, 4.38 mol) in tetrahydrofuran (8.0 mL) was added to the reaction. The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction was cooled to -78 °C, followed by addition of tert-butyllithium (1.70 M in hexane, 10.50 mL). The reaction was stirred for 30

minutes, followed by addition of 0.65 M of CuCN.2LiCl in tetrahydrofuran (14.0 mL). The reaction was stirred at -35 °C for 10 minutes, followed by addition of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**535**, 1.70 g, 5.64 mol, prepared as described in Example 10, Scheme 164) in tetrahydrofuran (10.0 mL). The reaction was allowed to warm to room temperature for 1 hour and 2 N HCl (30 mL) was added to the reaction mixture, then stirred for 30 minutes. The reaction was poured into aqueous ammonia and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified with silica gel column chromatography eluting with 30% ethyl acetate in hexane to give the desired compound (**P-0132**, 0.75 g, 33.1%). MS (ESI) $[M+H^+]^+$ = 401.1.

Example 12: Synthesis of 5-chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0155

[0161] 5-Chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **P-0155** was synthesized in 1 step as shown in Scheme 166.

Scheme 166



Step 1 – Preparation of 5-chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0155):

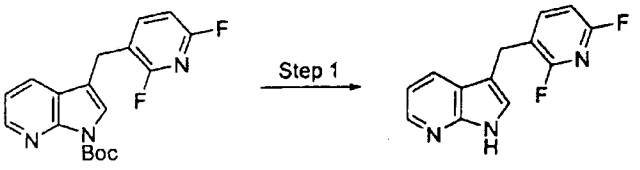
[0162] To 2,6-Difluoropyridine (**58**, 3.40 g, 0.0295 mol) in tetrahydrofuran (200.0 mL), under an atmosphere of nitrogen at -78 °C, 2.50 M of n-butyllithium in hexane (12.0 mL) was added slowly. After 60 minutes, CuCN.2LiCl (0.75 M in tetrahydrofuran, 40.0 mL) was added to the reaction mixture. After 5 minutes, 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**535**, 4.20 g, 0.0139 mol, prepared as described in Example 10, Scheme 164) in tetrahydrofuran (20 mL) was added to the reaction. The reaction was stirred at -78 °C overnight, then poured into water and ammonia (10 mL), and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 15% ethyl acetate in hexane to give a white solid (**P-0155**, 300 mg, 7.7%). MS (ESI) $[M-H^+]^-$ = 278.1.

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Example 13: Synthesis of 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0154

[0163] 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **P-0154** was synthesized in 1 step as shown in Scheme 167.

Scheme 167



536 **P-0154**

Step 1 – Preparation of 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0154):

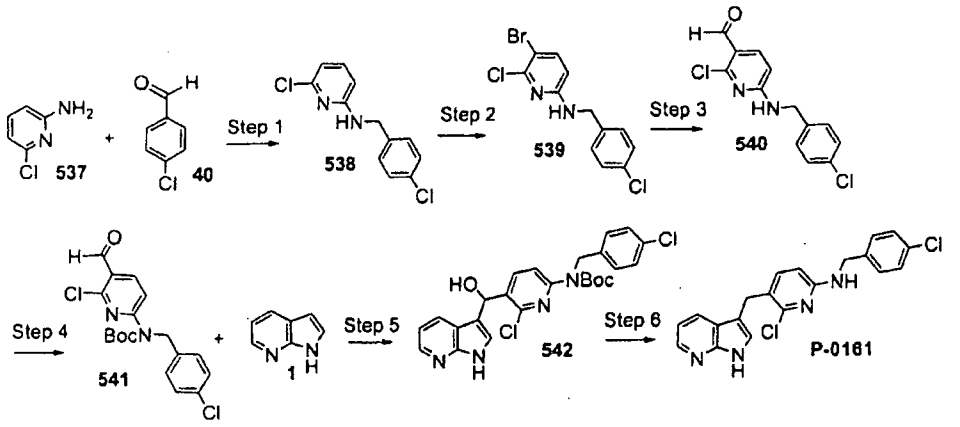
[0164] To 3-(2,6-difluoro-pyridin-3-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**536**, 0.35 g, 1.0 mmol, prepared as described in Example 10, Scheme 164, replacing 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 1H-pyrrolo[2,3-b]pyridine in step 1) in N-methylpyrrolidinone (3.00 mL) were added p-chlorobenzylamine (0.20 mL, 1.6 mmol) and N,N-diisopropylethylamine (0.30 mL, 0.0017 mol). The reaction was stirred at 50 °C for 72 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and the crude intermediate was dissolve in dichloromethane (15.0 mL) and trifluoroacetic acid (0.5 mL). The reaction was stirred at room temperature for 2 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 35% ethyl acetate in hexane to give a white solid (**P-0154**, 0.18 g, 72%). MS (ESI) $[M+H^+]^+ = 246.2$.

Example 14: Synthesis of 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine P-0161

[0165] 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine **P-0161** was synthesized in 6 steps as shown in Scheme 168.

Scheme 168

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Step 1 - Preparation of (4-chloro-benzyl)-(6-chloro-pyridin-2-yl)-amine (538):

[0166] To 6-chloro-pyridin-2-ylamine (**537**, 5.60 g, 0.0436 mol) in acetonitrile (300 mL) were added 4-chlorobenzaldehyde (**40**, 6.7 g, 0.048 mol), trifluoroacetic acid (13 mL, 0.17 mol) and tricthylsilane (21 mL, 0.13 mol). The reaction was heated to reflux for 4 hours, then concentrated, poured into water, extracted with ethyl acetate, and washed with sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The filtrate was purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**538**, 6.5 g, 59%). MS (ESI) $[M+H^+]^+ = 255.1$.

Step 2 – Preparation of (5-bromo-6-chloro-pyridin-2-yl)-(4-chloro-benzyl)-amine (539):

[0167] To (4-chloro-benzyl)-(6-chloro-pyridin-2-yl)-amine (**538**, 4.00 g, 0.0158 mol) in acetonitrile (66.7 mL, 1.28 mol) under an atmosphere of nitrogen, N-bromosuccinimide (2.81 g, 0.0158 mol) in acetonitrile (20 mL) 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, concentrated and crystallized with ethyl acetate in hexane to give a white solid (**539**, 2.60 g, 95.3%).

Step 3 – Preparation of 2-chloro-6-(4-chloro-benzylamino)-pyridine-3-carbaldehyde (540):

[0168] To (5-bromo-6-chloro-pyridin-2-yl)-(4-chloro-benzyl)-amine (**539**, 2.60 g, 7.83 mmol) in tetrahydrofuran (60.0 mL) under an atmosphere of nitrogen at -78 °C, isopropylmagnesium chloride (2.00 M in tetrahydrofuran, 4.20 mL) was added over 10 minutes. The reaction was stirred at -78 °C for 20 minutes, then allowed to warm to room temperature for 10 minutes. The reaction was cooled to -78 °C. tert-Butyllithium (1.70 M in hexane, 10.2 mL) was added to the reaction over 10 minutes. After 40 minutes, N,N-dimethylformamide (1.80 mL, 0.0232 mol) was added to the reaction. The reaction was stirred at -78 °C for 40 minutes, then allowed to warm to

room temperature for another 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, concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a light yellow solid (**540**, 1.0 g, 45.4%). MS (ESI) $[M-H^+]^-$ = 279.0.

Step 4 – Preparation of (4-chloro-benzyl)-(6-chloro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (541):

[0169] To 2-chloro-6-(4-chloro-benzylamino)-pyridine-3-carbaldehyde (**540**, 0.40 g, 1.42 mmol) in dichloromethane (10.0 mL) were added 4-dimethylaminopyridine (10.0 mg, 0.082 mmol), di-tert-butyldicarbonate (0.693 g, 3.17 mmol) and triethylamine (0.50 mL, 0.0036 mol). The reaction was stirred at room temperature overnight, then concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**541**, 0.45 g, 83.0%).

Step 5 – Preparation of (4-chloro-benzyl)-6-chloro-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (542):

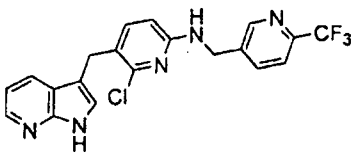
[0170] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 465 mg, 3.93 mmol) in methanol (50 mL) were added sodium hydroxide (0.630 g, 0.0157 mol) and (4-chloro-benzyl)-(6-chloro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**541**, 1.5 g, 0.0039 mol). The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**542**, 1.0g, 51%). MS (ESI) $[M+H^+]^+$ = 499.1.

Step 6 – Preparation of 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine (P-0161):

[0171] To (4-chloro-benzyl)-6-chloro-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (**542**, 1.00 g, 2.00 mmol) in acetonitrile (130.0 mL) were added triethylsilane (11.5 mL, 0.0720 mol) and trifluoroacetic acid (5.5 mL, 0.071 mol). The reaction was heated to reflux for 2 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give a light yellow solid (**P-0161**, 480 mg, 62%). MS (ESI) $[M+H^+]^+$ = 383.1, 385.1.

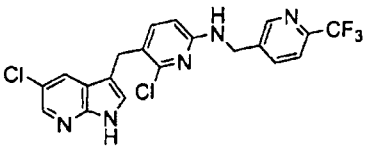
[0172] [6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0174**

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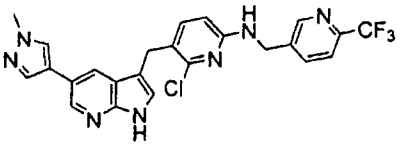
was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1. MS (ESI) $[M+H^+]^+ = 418.2$.

[0173] [6-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0176**



was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-chloro-1H-pyrrolo[2,3-b]pyridine in step 5. MS (ESI) $[M+H^+]^+ = 452.0$.

[0174] {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**

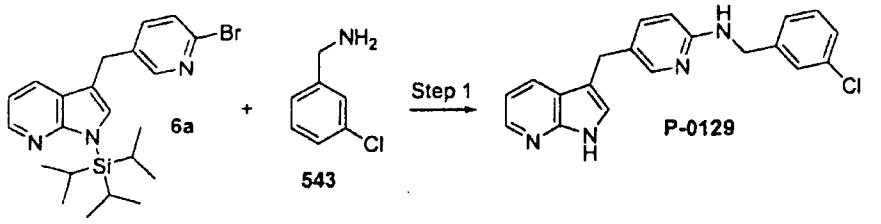


was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (prepared as described in Example 18, Scheme 172) in step 5. MS (ESI) $[M+H^+]^+ = 498.0$.

Example 15: Synthesis of (3-chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0129

[0175] (3-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0129** was synthesized in 1 step as shown in Scheme 169.

Scheme 169



Step 1 – Preparation of (3-chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0129):

[0176] 3-(6-bromo-pyridin-3-ylmethyl)-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6a**, 10 mg, 0.023 mmol) was combined with 3-chlorobenzyl amine (**543**, 13 mg, 0.093 mmol) in dioxane (0.3 mL). Tris(dibenzylideneacetone)-dipalladium(0) (3 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 3 mg) and sodium *tert*-butoxide (15 mg) were added. The mixture was heated at 100 °C overnight. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in DMSO and purified by reverse phase HPLC on a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 5-40% acetonitrile with 0.1% trifluoroacetic acid over 13 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0129**. MS (ESI) $[M+H^+]^+ = 349.1$.

[0177] Additional compounds were prepared following the protocol of Scheme 169, replacing 3-chlorobenzyl amine **543** with an appropriate amine. The following compounds were made following this procedure:

(4-Morpholin-4-ylmethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0093**),

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

(5-Methyl-isoxazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0095**),

(2-Pyrrolidin-1-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0096**),

[1-(4-Methanesulfonyl-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0097**),

(2-Methoxy-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0098**),

(2-Morpholin-4-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0099**),

((R)-1-Phenyl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0125**),

(3-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0126**),

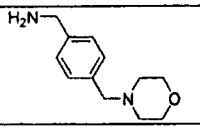
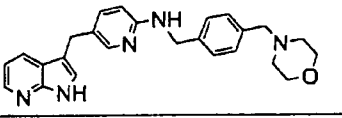
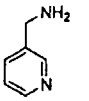
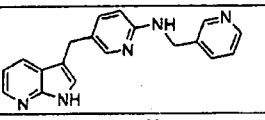
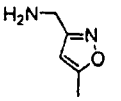
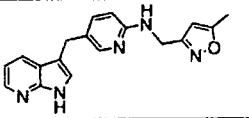
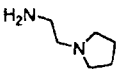
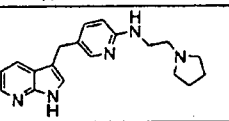
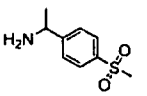
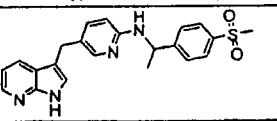
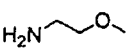
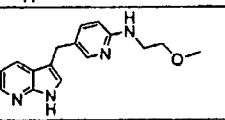
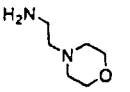
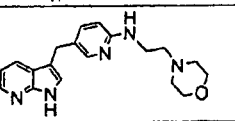
[1-(2-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0127**),

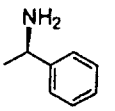
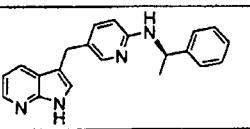
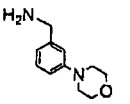
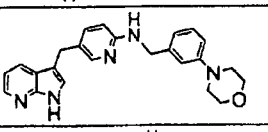
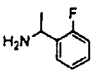
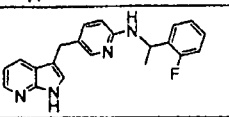
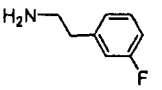
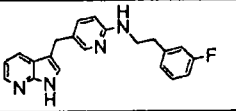
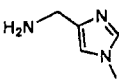
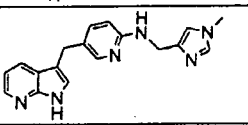
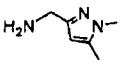
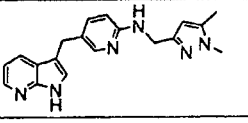
[2-(3-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0128**),

(1-Methyl-1H-imidazol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0130**), and

(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0131**).

[0178] The following table indicates the amine (Column 2) used in Scheme 169 to provide the compounds (Column 3). Column 1 provides the compound number and column 4 the observed mass.

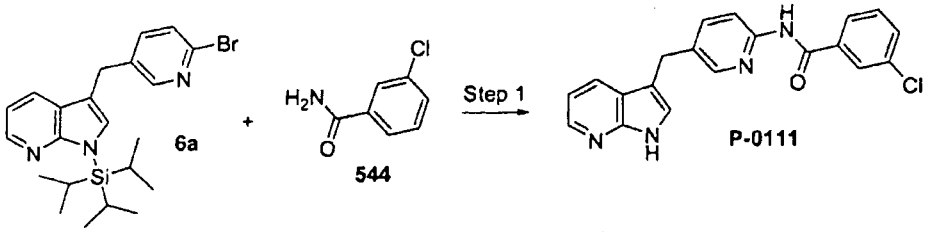
Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0093			414.3
P-0094			316.3
P-0095			319.9
P-0096			322.3
P-0097			407.1
P-0098			283.5
P-0099			338.3

Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0125			329.1
P-0126			400.3
P-0127			347.1
P-0128			347.1
P-0130			319.1
P-0131			333.1

Example 16: Synthesis of 3-chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide P-0111

[0179] 3-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **P-0111** was synthesized in 1 step as shown in Scheme 170.

Scheme 170



*Step 1 – Preparation of 3-chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0111**):*

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[0180] 3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6a**, 10 mg, 0.023 mmol) was combined with 3-chloro-benzamide (**544**, 15 mg, 0.096 mmol) in dioxane (0.4 mL). Tris(dibenzylideneacetone)-dipalladium(0) (3 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 3 mg), and sodium *tert*-butoxide (15 mg) were added. Cesium carbonate (20 mg) was added and the mixture was heated at 100 °C overnight. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in DMSO (0.2 mL) and purified by reverse phase HPLC on a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 5-40% acetonitrile with 0.1% trifluoroacetic acid over 13 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0111**. MS (ESI) $[M+H^+]^+ = 363.1$.

[0181] Additional compounds were prepared following the protocol of Scheme 170, replacing 3-chloro-benzamide **544** with an appropriate amide. The following compounds were made following this procedure:

3,4-Dichloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0100**),

2-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0101**),

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0102**),

Thiophene-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0103**),

2-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0104**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0105**),

Pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0106**),

Pyridine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0107**),

6-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-nicotinamide (**P-0108**),

4-Fluoro-3-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0109**),

5-Methyl-pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0110**),

4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0112**),

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N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethoxy-benzamide (**P-0113**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0114**),

3-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0115**),

3,4-Difluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0116**),

2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0117**),

5-Fluoro-2-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0118**),

2-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0119**),

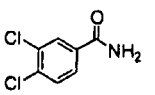
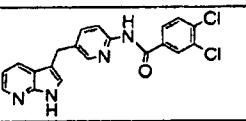
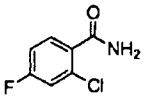
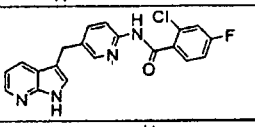
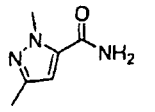
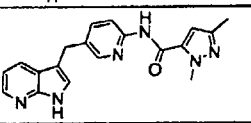
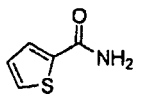
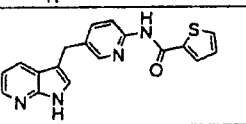
3-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0120**),

3-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0121**),

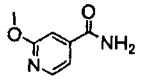
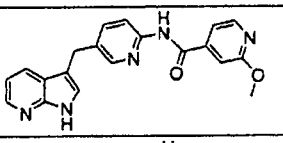
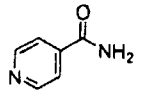
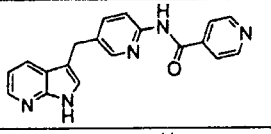
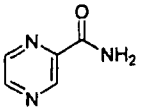
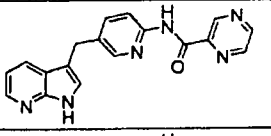
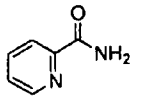
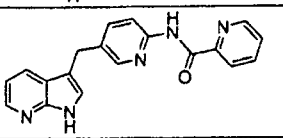
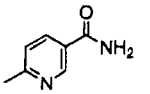
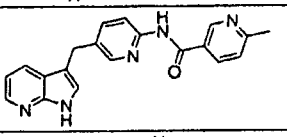
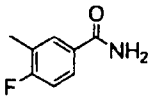
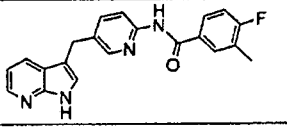
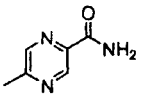
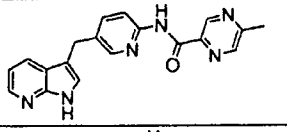
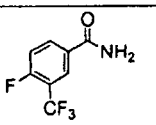
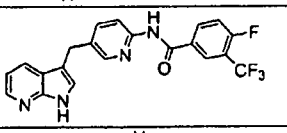
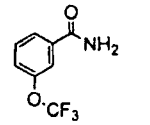
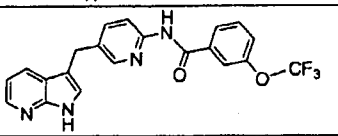
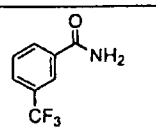
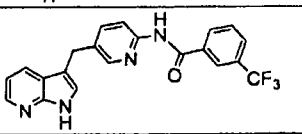
3-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0122**), and

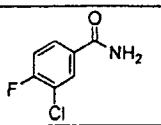
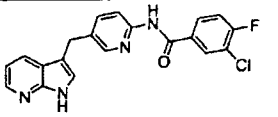
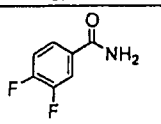
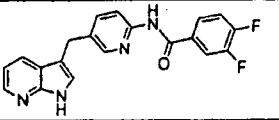
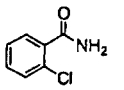
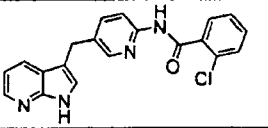
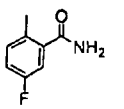
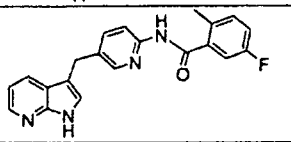
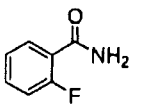
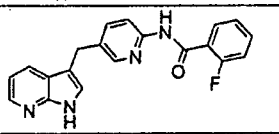
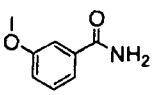
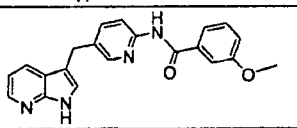
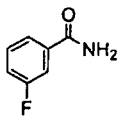
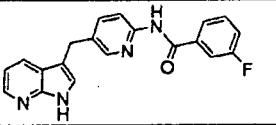
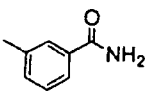
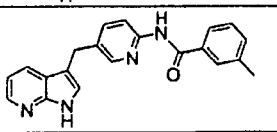
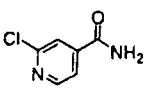
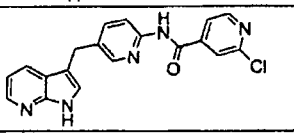
2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0123**).

[0182] The following table indicates the amide (Column 2) used in Scheme 170 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0100			397.1
P-0101			381.1
P-0102			347.1
P-0103			335.1

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Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0104			360.3
P-0105			329.9
P-0106			331.1
P-0107			329.9
P-0108			344.3
P-0109			361.1
P-0110			345.1
P-0112			415.1
P-0113			413.1
P-0114			397.1

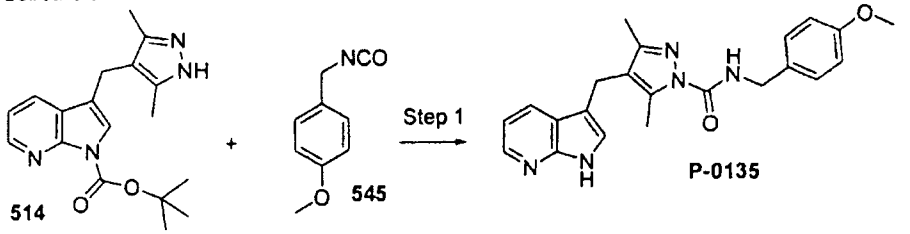
Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0115			381.1
P-0116			365.1
P-0117			363.1
P-0118			361.1
P-0119			347.1
P-0120			359.1
P-0121			347.1
P-0122			343.1
P-0123			364.3

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Example 17: Synthesis of 3,5-dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide P-0135

[0183] 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide **P-0135** was synthesized in 1 step as shown in Scheme 171.

Scheme 171



*Step 1 – Preparation of 3,5-dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide (**P-0135**):*

[0184] 3-(3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 10 mg, 0.03 mmol) was dissolved in dichloromethane (0.5 mL). 1,8-Diazabicylo[5.4.0]unde-7-ene (6 mg, 0.04 mmol) was added. 1-Isocyanatomethyl-4-methoxy-benzene (**545**, 6.5 mg, 0.04 mmol) was added. The reaction was allowed to proceed at room temperature for 30 minutes. Acetic acid (0.2 mL) was added to the reaciton. The solvents were removed under reduced pressure. The residue was dissolved in dimethyl sulfoxide (0.2 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 20-100% acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0135**. MS (ESI) $[M+H^+]^+ = 390.3$.

[0185] Additional compounds were prepared following the protocol of Scheme 171, replacing 1-isocyanatomethyl-4-methoxy-benzene **545** with an appropriate isocyanate or bromide. The following compounds were made following this procedure:

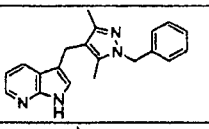
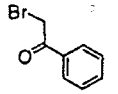
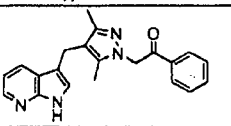
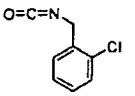
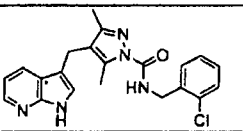
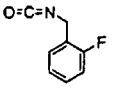
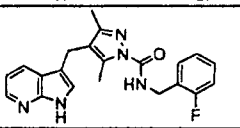
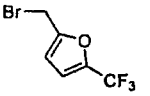
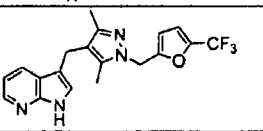
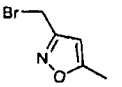
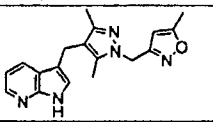
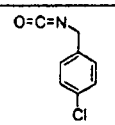
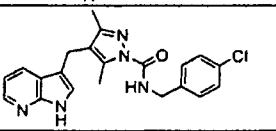
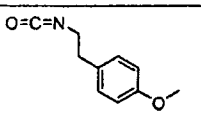
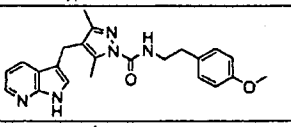
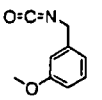
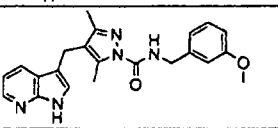
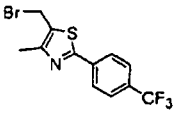
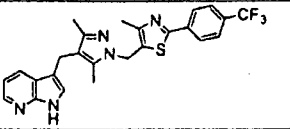
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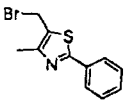
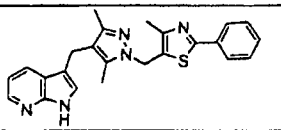
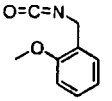
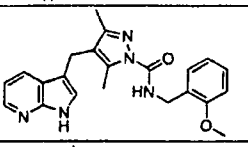
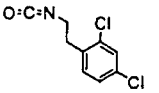
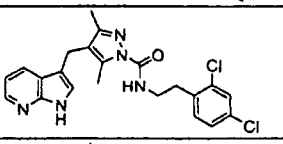
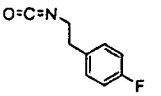
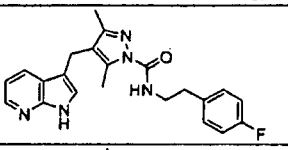
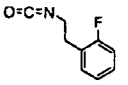
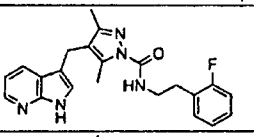
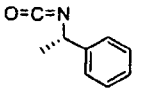
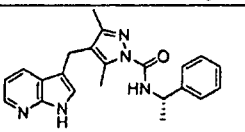
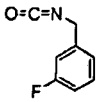
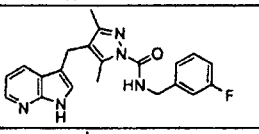
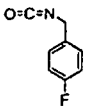
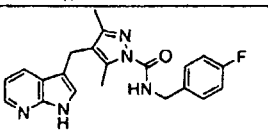
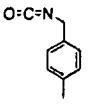
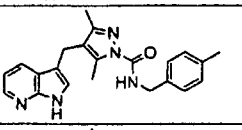
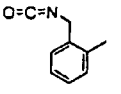
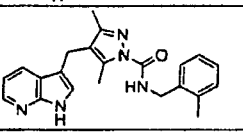
2-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-1-phenyl-ethanone (**P-0134**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-chloro-benzylamide (**P-0136**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-fluoro-benzylamide (**P-0137**),
3-[3,5-Dimethyl-1-(5-trifluoromethyl-furan-2-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0138**),
3-[3,5-Dimethyl-1-(5-methyl-isoxazol-3-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0139**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-chloro-benzylamide (**P-0140**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-ethoxy-phenyl)-ethyl]-amide (**P-0141**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-methoxy-benzylamide (**P-0142**),
3-{3,5-Dimethyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-pyrazol-4-ylmethyl}-1H-pyrrolo[2,3-b]pyridine (**P-0143**),
3-[3,5-Dimethyl-1-(4-methyl-2-phenyl-thiazol-5-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0144**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methoxy-benzylamide (**P-0145**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide (**P-0146**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide (**P-0147**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide (**P-0148**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid ((S)-1-phenyl-ethyl)-amide (**P-0149**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-fluoro-benzylamide (**P-0150**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-fluoro-benzylamide (**P-0151**),
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methyl-benzylamide (**P-0152**), and
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methyl-benzylamide (**P-0153**).

[0186] The following table indicates the isocyanate or bromide (Column 2) used in Scheme 171 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

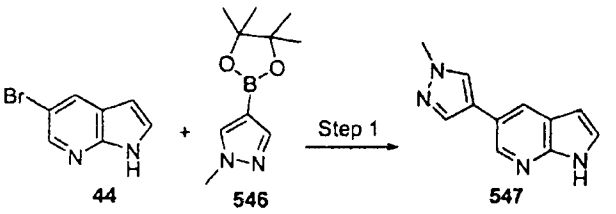
Compound number	Isocyanate or bromide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0133			317.1
P-0134			345.1
P-0136			394.3
P-0137			378.3
P-0138			375.1
P-0139			322.3
P-0140			393.9
P-0141			404.3
P-0142			390.3
P-0143			482.3

Compound number	Isocyanate or bromide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0144			414.3
P-0145			390.3
P-0146			442.3
P-0147			392.3
P-0148			392.3
P-0149			374.3
P-0150			378.3
P-0151			378.3
P-0152			374.3
P-0153			374.3

Example 18: Synthesis of 5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine 547.

[0187] 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **547** was synthesized in 1 step from 5-bromo-1H-pyrrolo[2,3-b]pyridine **44** as shown in Scheme 172.

Scheme 172



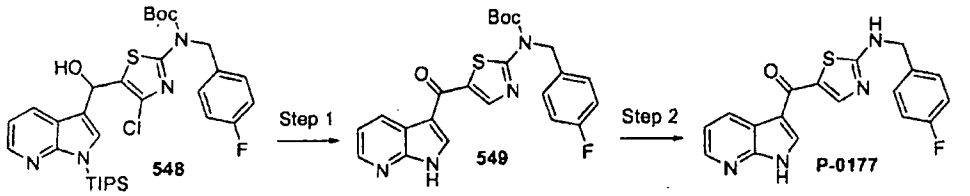
Step 1 - Preparation of 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**547**):

[0188] To 5-bromo-7-azaindole (**44**, 1.04 g, 5.28 mmol) in 1.00 M potassium carbonate in water (15.8 mL) and tetrahydrofuran (50.0 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (**546**, 1.65 g, 7.92 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.305 mg, 0.26 mmol) and tetra-n-butylammonium iodide (0.20 g, 0.53 mmol). The reaction mixture was stirred at 70 °C overnight. The reaction mixture was poured into water and the organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide a light yellow solid (**547**, 670 mg, 64.0%). MS(ESI)$[M+H^+]^+$ = 199.4.

Example 19: Synthesis of [2-(4-fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0177.

[0189] [2-(4-Fluoro-benzylamino)-thiazol-5 -yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0177** was synthesized in 2 steps as shown in Scheme 173.

Scheme 173



Step 1 – Preparation of(4-fluoro-benzyl)-[5-(1H-pyrrolo[2, 3-b]pyridine-3-carbonyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (549):

[0190] A mixture of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**548**, 0.397 g, 0.57 mmol, prepared according to the protocol of Scheme 159, Example 5, replacing 4-(aminomethyl)pyridine **516** with 4-fluoro-benzylamine in step 1, isolated after step 3), triethylsilane (1.0 mL, 6.3 mmol), and trifluoroacetic acid (0.5 mL, 6 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate and brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**549**, 0.11 g, 9%). MS (ESI) $[M-H^+]^+ = 451.10$.

Step 2 – Preparation of [2-(4-fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0177):

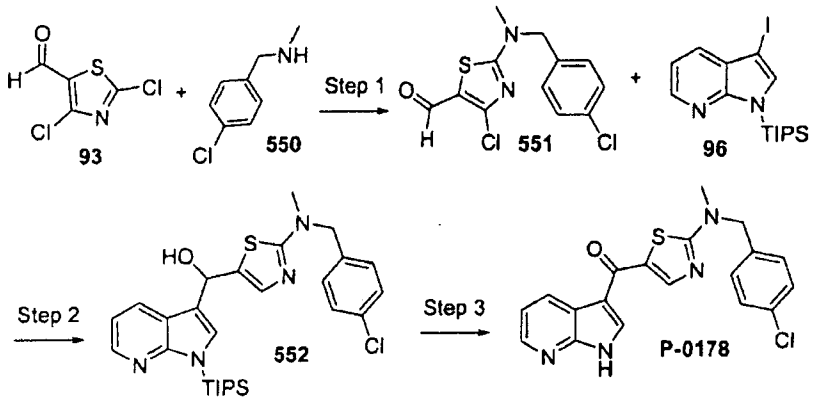
[0191] To a solution of (4-fluoro-benzyl)-[5-(1H-pyrrolo[2, 3-b]pyridine-3-carbonyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (**549**, 0.11g, 0.2 mmol) in dichloromethane (2 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into cold sodium bicarbonate solution, extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After removal of solvents, the residue was washed with ethyl acetate to provide the desired compound as a yellow solid (**P-0177**, 9 mg, 10%). MS (ESI) $[M+H^+]^+ = 353.12$.

Example 20: Synthesis of {2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0178.

[0192] {2-[(4-Chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0178** was synthesized in 3 steps as shown in Scheme 174.

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Scheme 174



Step 1 – Preparation of 4-chloro-2-[(4-chloro-benzyl)-methy l-amino]-thiazole-5-carbaldehyde (551):

[0193] To a solution of (4-chloro-benzyl)-methyl-amine (**550**, 2 g, 0.01 mol) and N,N-diisopropylethylamine (4 mL, 0.03 mol) in tetrahydrofuran (50 mL) was added 2,4-dichloro-thiazole-5-carbaldehyde (**93**, 3 g, 0.01 mmmol) in tetrahydrofuran (20 mL) 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, and dried over sodium sulfate. After removal of solvent, the residue was collected by filtration and washed with hexanes to provide the desired compound as a light-yellow solid (**551**, 3.6 g, 90%).

Step 2 – Preparation of {4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (552):

[0194] To a solution of 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.82 g, 2.0 mmol) in tetrahydrofuran (5 mL) at -20 °C, isopropylmagnesium chloride (2 M in tetrahydrofuran, 1.1 mL, 2.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C in 10 minutes. The reaction mixture was then cooled to -40 °C. To the reaction mixture was added a solution of 4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazole-5-carbaldehyde (**551**, 0.41 g, 1.4 mmol) in tetrahydrofuran (10 mL). The reaction mixture was allowed to warm to -10 °C in 30 minutes. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**552**, 0.5 g, 60%). MS (ESI) $[M+H^+]^+ = 575.29$.

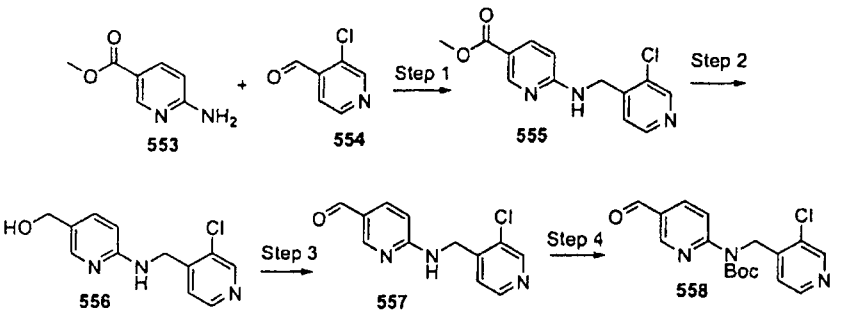
*Step 3 – Preparation of {2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0178**):*

[0195] A mixture of {4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**552**, 1 g, 2 mmol), triethylsilane (2 mL, 12 mmol), and trifluoroacetic acid (1 mL, 13 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate and brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**P-0178**, 0.17 g, 30%). MS (ESI) $[M+H^+]^+ = 383.09$.

Example 21: Synthesis of aldehyde intermediates.

[0196] (3-Chloro-pyridin-4-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **558** was synthesized in 4 steps from 6-amino-nicotinic acid methyl ester **553** as shown in Scheme 175.

Scheme 175



Step 1 – Synthesis of 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (555):

[0197] To 6-amino-nicotinic acid methyl ester (**553**, 2.15 g, 0.014 mol) in acetonitrile (60.0 mL) were added 3-chloro-pyridine-4-carbaldehyde (**554**, 2.00 g, 0.014 mol), triethylsilane (11.00 mL, 0.069 mol) and trifluoroacetic acid (5.00 mL, 0.065 mol). The reaction was stirred at 80 °C overnight. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**555**, 1.5 g, 38.2%). MS (ESI) $[M+H^+]^+ = 278.9$.

Step 2 – Synthesis of 6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-yl-methanol (556):

[0198] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (**555**, 1.00 g, 3.60 mmol) in tetrahydrofuran (120 mL) was added a solution of lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 5.00 mL) under an atmosphere of nitrogen at room temperature. The reaction

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was stirred at room temperature overnight, followed with addition of sodium sulfate decahydrate. After 1 hour, the reaction mixture was filtered, concentrated, and purified with silica gel column chromatography eluting with 2% to 20% methanol in dichloromethane to give the desired compound as a white solid (**556**, 0.5 g, 56%). MS (ESI) $[M+H^+]^+ = 250.1$.

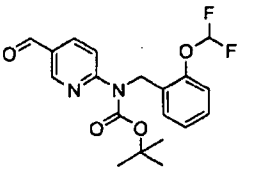
Step 3 – Synthesis of 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridine-3-carbaldehyde (557):

[0199] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-yl-methanol (**556**, 0.50 g, 2.00 mmol) in tetrahydrofuran (20.0 mL) was added Dess-Martin periodinane (1.02 g, 2.40 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude compound (**557**, 0.45 g, 91%) that was used in the next step without further purification.

Step 4 – Synthesis of (3-chloro-pyridin-4-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (558):

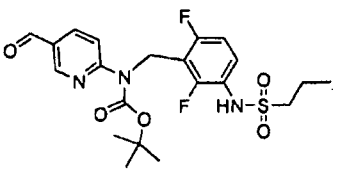
[0200] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridine-3-carbaldehyde (**557**, 0.45 g, 1.80 mmol) in dichloromethane (20.0 mL) were added di-tert-butyldicarbonate (0.65 g, 3.00mmol), 4-dimethylaminopyridine (0.012 g, 0.010 mmol) and triethylamine (0.28 mL, 2.00 mmol). The reaction was stirred at room temperature overnight, then concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**558**, 250 mg, 40.0%).

[0201] (2-Difluoromethoxy-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **559**



was prepared following the protocol of Scheme 175, substituting 3-chloro-pyridine-4-carbaldehyde **554** with 2-difluoromethoxy-benzaldehyde in Step 1.

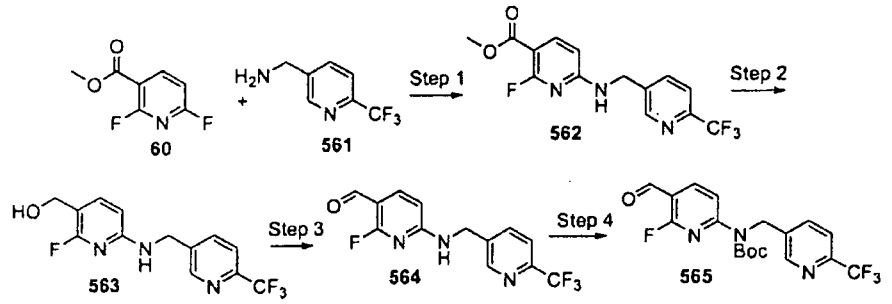
[0202] [2,6-Difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **560**



was prepared following the protocol of Scheme 175, substituting 3-chloro-pyridine-4-carbaldehyde **554** with propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide in Step 1. MS (ESI) $[M+H^+]^+ = 470.3$.

[0203] (6-Fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **565** was synthesized in 4 steps from 2,6-Difluoro-nicotinic acid methyl ester **60** as shown in Scheme 176.

Scheme 176



Step 1 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (562):

[0204] To 2,6-difluoro-nicotinic acid methyl ester (**60**, 1.82 g, 0.0105 mol) in N,N-dimethylformamide (20.0 mL), under an atmosphere of nitrogen at -40 °C, C-(6-trifluoromethyl-pyridin-3-yl)-methylamine (**561**, 1.00 g, 5.68 mmol) was added. The reaction was stirred at -40 °C, then allowed to warm to room temperature for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a white solid (**562**, 1.40 g, 74.9). MS (ESI) $[M+H^+]^+ = 330.1$.

Step 2 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanol (563):

[0205] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (**562**, 1.40 g, 4.25 mmol) in tetrahydrofuran (100.0 mL) under an atmosphere of nitrogen at room temperature, a solution of lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 10.0 mL) was added slowly. The reaction was stirred at room temperature overnight, followed by addition of an appropriate amount of sodium sulfate decahydrate. After 1 hour, the reaction mixture was filtered and concentrated to give crude compound (**563**, 1.2 g, 93.7%) that was used in the next step without further purification.

Step 3 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (564):

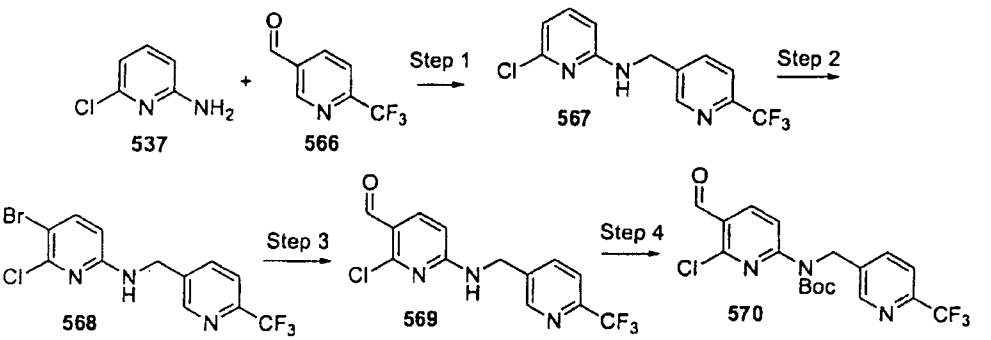
[0206] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanol (**563**, 1.20 g, 3.98 mmol) in dichloromethane (40.0 mL) was added Dess-Martin periodinane (1.86 g, 4.38 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous sodium thiosulfate and potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**564**, 0.28 g, 23.5%).

Step 4 – Synthesis of (6-fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (565):

[0207] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (**564**, 0.28 g, 0.94 mmol) in tetrahydrofuran (10.0 mL) were added di-tert-butyldicarbonate (0.245 g, 1.12 mmol) and 4-dimethylaminopyridine (0.050 g, 0.41 mmol). The reaction was stirred at room temperature overnight, then concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**565**, 0.22 g, 59%).

[0208] (6-Chloro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **570** was synthesized in 4 steps from 6-chloro-pyridin-2-ylamine **537** as shown in Scheme 177.

Scheme 177



Step 1 – Synthesis of (6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (567):

[0209] To 6-chloro-pyridin-2-ylamine (**537**, 0.760 g, 5.91 mmol) in acetonitrile (30.0 mL), 6-trifluoromethyl-pyridine-3-carbaldehyde (**566**, 1.06 g, 6.05 mmol), trifluoroacetic acid (3.00 mL,

0.0389 mol) and triethylsilane (6.00 mL, 0.0376 mol) were added. The reaction was heated to reflux for 4 hours. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**567**, 1.60 g, 94.1%).

Step 2 – Synthesis of (5-bromo-6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (568):

[0210] To (6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**567**, 4.50 g, 0.0156 mol) in acetonitrile (120.0 mL) under an atmosphere of nitrogen, N-bromosuccinimide (3.03 g, 0.0170 mol) in acetonitrile (50 mL) 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, concentrated and purified with silica gel column chromatography eluting with 25% to 100% ethyl acetate in hexane to give a white solid (**568**, 6.20 g, 80.2%).

Step 3 – Synthesis of 2-chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (569):

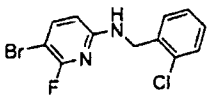
[0211] To (5-bromo-6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**568**, 4.60 g, 0.0125 mol) in tetrahydrofuran (60.0 mL) under an atmosphere of nitrogen at -78 °C, isopropylmagnesium chloride (2.00 M in tetrahydrofuran, 6.44 mL) was added over 10 minutes. The reaction was stirred at -78 °C for 20 minutes, and then allowed to warm to room temperature for 10 minutes. The reaction was cooled to -78 °C, followed by adding tert-butyllithium (1.70 M in hexane, 15.3 mL) over 10 minutes. After 40 minutes, N,N-dimethylformamide (1.23 mL, 0.0158 mol) was added and the reaction was stirred at -78 °C for 40 minutes, then allowed to warm to room temperature for 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, concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a light yellow solid (**569**, 2.84 g, 71.7%).

Step 4 – Synthesis of (6-chloro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (570)

[0212] To a solution of 2-chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (**569**, 0.545 g, 1.73 mmol) in tetrahydrofuran (10 mL), N,N-diisopropylethylamine (0.60 mL, 3.40 mmol), 4-dimethylaminopyridine (20 mg, 0.10 mmol), and a solution of di-tert-butyldicarbonate (0.41 g, 0.0019 mol) were added. The reaction mixture was stirred at room temperature overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica

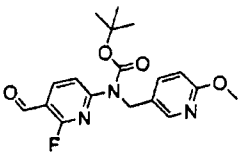
gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (570, 0.60 g, 83.6%).

[0213] (5-Bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine **571**



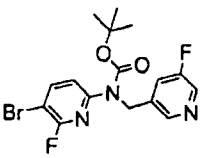
was prepared following the protocol of Steps 1 and 2 of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 2-chloro-benzaldehyde, respectively in Step 1.

[0214] (6-Fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **572**



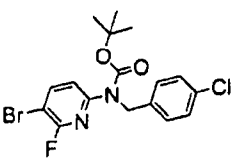
was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 6-methoxy-pyridine-3-carbaldehyde, respectively in Step 1.

[0215] (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **631**



was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 5-fluoro-pyridine-3-carbaldehyde, respectively in Step 1, without Step 3 (i.e. the product of Step 2 is reacted according to Step 4).

[0216] (5-Bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester **637**



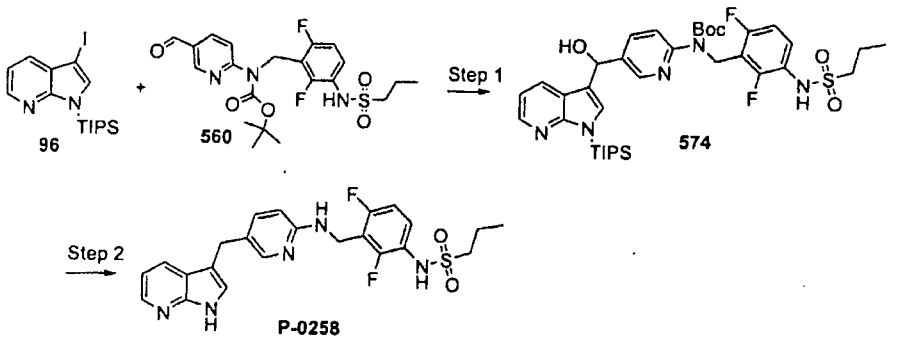
125

was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 5-chloro-benzaldehyde, respectively in Step 1, without Step 3 (i.e. the product of Step 2 is reacted according to Step 4).

Example 22: Synthesis of propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide P-0258

[0217] Propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide **P-0258** was synthesized in 2 steps from 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** as shown in Scheme 178.

Scheme 178



Step 1 – Synthesis of [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyr idin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (574):

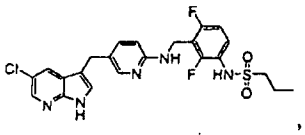
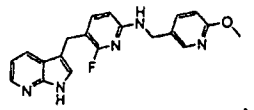
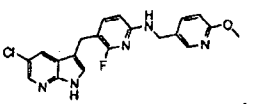
[0218] To a solution of 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.644 g, 1.61 mmol) in tetrahydrofuran (10.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.80 mL) was added slowly. The reaction was allowed to warm to 15 °C over 100 minutes, then cooled to -40 °C, followed by adding [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**560**, 0.100 g, 0.21 mmol, prepared as described in Example 21, Scheme 175) in tetrahydrofuran (2.0 mL). The reaction was allowed to warm to 5 °C over 2 hours, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow solid (**574**, 75 mg, 47%). MS (ESI) $[M+H^+]^+ = 744.7$.

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Step 2 – Synthesis of Propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide (P-0258):

[0219] To [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyr idin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (**574**, 75.0 mg, 0.10 mmol) in acetonitrile (10.0 mL) were added triethylsilane (0.40 mL, 2.5 mmol) and trifluoroacetic acid (0.20 mL, 2.6 mmol). The reaction was stirred at 80 °C for 4 hours. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give an off-white solid (**P-0258**, 29.3 mg, 61.6%). MS (ESI) $[M+H^+]^+ = 472.4$.

[0220] Propane-1-sulfonic acid (3-{[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-2,4-difluoro-phenyl)-amide (**P-0259**), [6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0378**), and [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0379**),

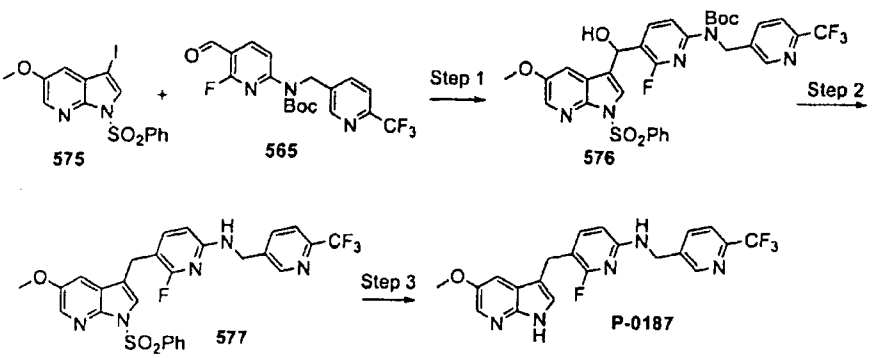

, 
, and 
,

respectively, were prepared following the protocol of Scheme 178. **P-0259** was prepared by replacing 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** with 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine in Step 1 (MS $[M+H^+]^+ = 506.1$). **P-0378** was prepared by replacing [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **560** with (6-Fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **572** (prepared as described in Example 21, Scheme 177) in Step 1 (MS $[M+H^+]^+ = 364.1$). **P-0379** was prepared by replacing both azaindole **96** with 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine and aldehyde **560** with aldehyde **572** in Step 1 (MS $[M+H^+]^+ = 400.0$).

Example 23: Synthesis of [6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine P-0187

[0221] [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0187** was synthesized in 3 steps from 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **575** as shown in Scheme 179.

Scheme 179



Step 1 - Synthesis of 5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (576):

[0222] To 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**575**, 0.326 g, 0.000788 mol) in tetrahydrofuran (3.00 mL) at -45 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.380 mL) was added slowly. The reaction was allowed to warm to -25 °C in 30 minutes, and then cooled to -45 °C followed by adding (6-fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**565**, 80.0 mg, 0.20 mmol, prepared as described in Example 21, Scheme 176) in tetrahydrofuran (1.0 mL). The reaction was allowed to warm to room temperature over 2 hours. The reaction was poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**576**, 0.080 g, 60%). MS (ESI) $[M+H^+]^+ = 688.1$.

Step 2 – Synthesis of [5-(1-Benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (577):

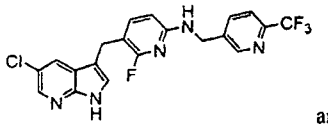
[0223] To 5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**576**, 0.100 g, 0.15 mmol) in acetonitrile (12.6 mL) were added triethylsilane (0.34 mL, 2.10 mmol) and trifluoroacetic acid (0.17 mL, 2.20 mmol). The reaction was heated to 80 °C for 2 hours. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give the crude compound (**577**, 90 mg, 100%) that was used in the next step without further purification.

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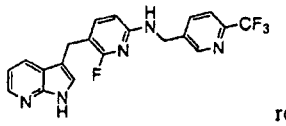
Step 3 – Synthesis of [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (P-0187):

[0224] To [5-(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**577**, 0.08 g, 0.13 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.110 g, 0.35 mmol). The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give an off-white solid (**P-0187**, 8.1 mg, 10%). MS (ESI) $[M+H^+]^+ = 431.9$.

[0225] [6-Fluoro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0186** and [6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0188**,



and



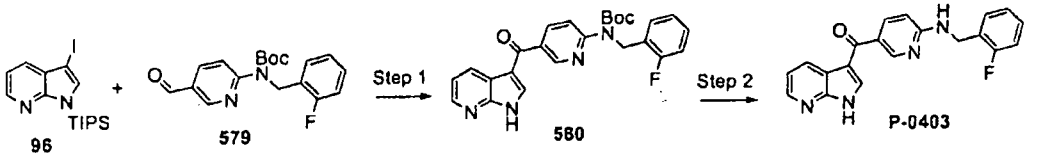
respectively,

were prepared following the protocol of Scheme 179, substituting 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **575** with 1-benzenesulfonyl-3-iodo-5-chloro-1H-pyrrolo[2,3-b]pyridine or 1-Benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine, respectively, in Step 1. MS (ESI) $[M+H^+]^+ = 435.7$ and 401.6, respectively.

Example 24: Synthesis of [6-(2-fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0403

[0226] Synthesis of [6-(2-fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0403** was synthesized in 2 steps from 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** as shown in Scheme 180.

Scheme 180



Step 1 – (2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic

acid tert-butyl ester (580):

[0227] To 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.550 g, 1.37 mmol) in tetrahydrofuran (15.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.65 mL) was added slowly. The reaction was allowed to warm to 5 °C over 70 minutes, then cooled to -40 °C, followed by adding (2-fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**579**, prepared according to the protocol of Example 1, Scheme 19, Steps 1-3, replacing 4-chlorobenzaldehyde 40 with 2-fluoro-benzaldehyde in Step 1) in tetrahydrofuran (4.0 mL). 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 anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**580**, 0.14 g, 26%). MS (ESI) $[M+H^+]^+ = 447.0$.

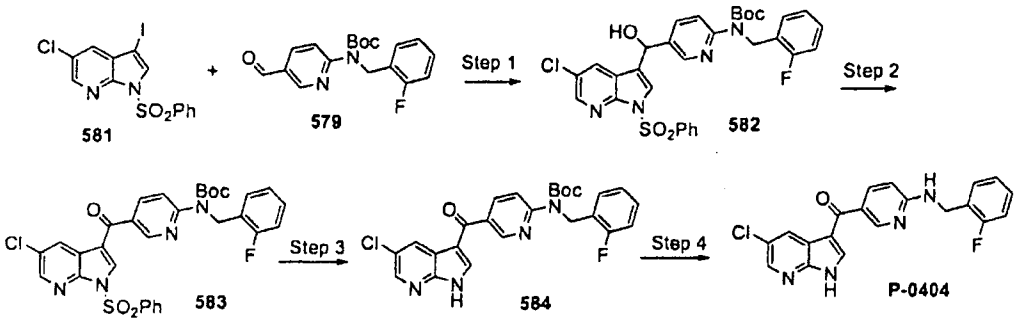
*Step 2 - Synthesis of [6-(2-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0403**):*

[0228] To (2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic acid tert-butyl ester (**580**, 0.080 g, 0.18 mmol) in dichloromethane (3.0 mL) was added trifluoroacetic acid (1.0 mL, 0.013 mol). The reaction was stirred at room temperature overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15 % methanol in dichloromethane to give the desired compound (**P-0403**, 15.0 mg, 23.0%). MS (ESI) $[M+H^+]^+ = 347.5$.

Example 25: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone P-0404

[0229] (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone **P-0404** was synthesized in 4 steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** as shown in Scheme 181.

Scheme 181



Step 1 – Synthesis of 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (582)

[0230] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 0.420 g, 1.00 mmol) in tetrahydrofuran (15.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.49 mL) was added slowly. The reaction was allowed to warm to 5 °C over 70 minutes, then cooled to -40 °C, followed by adding (2-fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **579** in tetrahydrofuran (6.0 mL). 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 anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**582**, 0.25 g, 41%). MS (ESI) $[M+H^+]^+ = 623.1$.

Step 2 – Synthesis of [5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (583):

[0231] To 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**582**, 0.25 g, 0.40 mmol) in dichloromethane (5.0 mL) was added Dess-Martin periodinane (0.20 g, 0.48 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**583**, 0.060 g., 24%).

Step 3 – Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (584):

[0232] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-

(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**583**, 60.0 mg, 0.097 mmol) in tetrahydrofuran (1.0 mL) was added aqueous potassium carbonate (1.0 M, 1.0 mL). The reaction was irradiated with microwave on 300 watts, 100°C for 10 minutes, then 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 (**584**, 0.040 g, 64%) that was used in the next step without further purification.

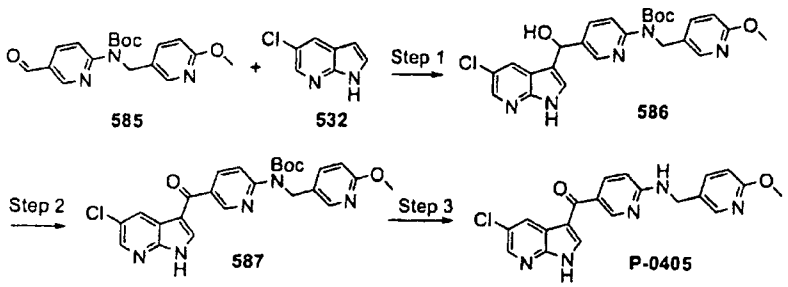
*Step 4 – Synthesis of (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone (**P-0404**):*

[0233] To [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**584**, 0.030 g, 0.062 mmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (1.0 mL, 0.013 mol). The reaction was stirred at room temperature overnight, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give the desired compound (**P-0404**, 2.8 mg, 12%). MS (ESI) $[M+H^+]^+ = 381.0$.

Example 26: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone P-0405

[0234] (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone **P-0405** was synthesized in 3 steps from 5-Chloro-1H-pyrrolo[2,3-b]pyridine **532** as shown in Scheme 182.

Scheme 182



Step 1 – Synthesis of 5-[(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (586):

[0235] To 5-chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 0.092 g, 0.60 mmol) in methanol (15.0 mL) were added (5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester

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(**585**, 0.240 g, 0.70 mmol, prepared according to the protocol of Example 1, Scheme 19, Steps 1-3, replacing 4-chlorobenzaldehyde **40** with 6-methoxy-pyridine-3-carbaldehyde in Step 1) and potassium hydroxide (1.2 g, 0.021 mol). The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**586**, 0.110 g, 37%).

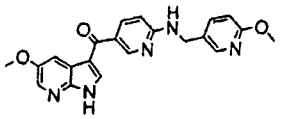
*Step 2 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**587**):*

[0236] To 5-[(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**586**, 0.060 g, 0.12 mmol) in dichloromethane (10.0 mL) was added Dess-Martin periodinane (0.062 g, 0.15 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction was concentrated and purified with a silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**587**, 0.020 g, 33%).

*Step 3 – Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone (**P-0405**):*

[0237] To [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**587**, 0.020 g, 0.040 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at room temperature for 2 hours, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0405**, 5.5 mg, 34%). MS (ESI) $[M+H^+]^+$ = 394.3.

[0238] {6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0406**

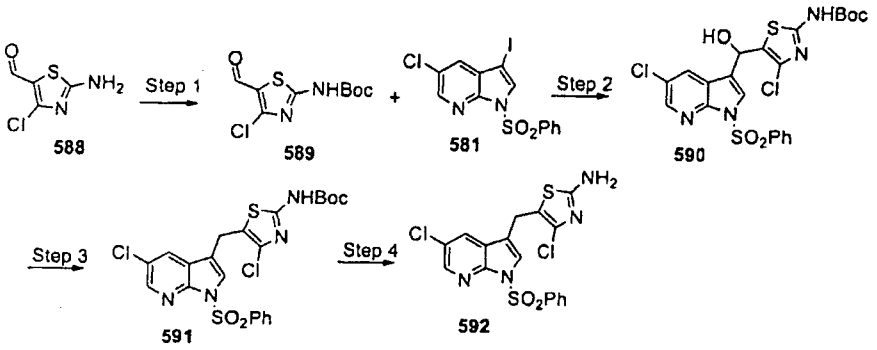


was prepared following the protocol of Scheme 182, substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 5-methoxy-1H-pyrrolo[2,3-b]pyridine in step 1. MS (ESI) $[M+H^+]^+$ = 390.1.

Example 27: Synthesis of intermediate 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine 592

[0239] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** was synthesized in 4 steps from 2-amino-4-chloro-thiazole-5-carbaldehyde **588** as shown in Scheme 183.

Scheme 183



Step 1 – Synthesis of (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (589):

[0240] To 2-amino-4-chloro-thiazole-5-carbaldehyde (**588**, 5.00 g, 0.0308 mol) in tetrahydrofuran (122 mL) were added di-tert-butyldicarbonate (7.38 g, 0.0338 mol) and 4-dimethylaminopyridine (0.35 g, 0.0029 mol). The reaction was stirred at 58 °C for 2 hours, then concentrated and purified with silica gel column chromatography eluting with 20% to 80% ethyl acetate in hexane to give a yellow solid (**589**, 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 (590):

[0241] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 4.40 g, 10.5 mmol) in tetrahydrofuran (30.0 mL) at -45 °C under nitrogen, a solution of isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 5.4 mL) was added slowly over 10 minutes. The reaction was allowed to warm to -25 °C over 30 minutes. The reaction was cooled to -65 °C, followed by adding the cold deprotonated (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester **589**, which was prepared in situ by adding isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 5.0 mL) to (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**589**, 2.51 g, 9.55 mmol) in tetrahydrofuran (23.0 mL) at -78 °C under an atmosphere of nitrogen. The reaction was allowed to warm to room temperature in 2 hours, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous

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sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25%to 100% ethyl acetate in hexane to give the desired compound (**590**, 3.70 g, 60.3%). MS (ESI) $[M+H^+]^+ = 554.2$.

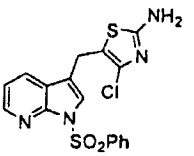
Step 3 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (591):

[0242] 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 (**590**, 0.200 g, 0.32 mmol) in dichloromethane (15.0 mL) were added triethylsilane (0.600 mL, 376 mmol) and trifluoroacetic acid (0.300 mL, 3.89 mmol). 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 and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25%to 100% ethyl acetate in hexane to give the desired compound (**591**, 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 (592):

[0243] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (**591**, 4.30 g, 7.97 mmol) in dichloromethane (70.0 mL) was added a solution of hydrogen chloride (4.00 M in 1,4-dioxane, 42.0 mL). The reaction was stirred at room temperature for 2 days, then concentrated, and titrated with ethyl ether and ethyl acetate to give the desired compound (**592**, 2.60 g, 74.2%). MS (ESI) $[M+H^+]^+ = 439.0$.

[0244] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **593**

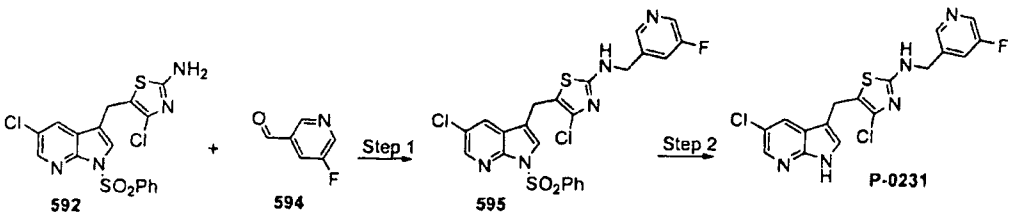


was prepared following the protocol of Scheme 183, substituting 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** with 1-benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine in Step 2. MS (ESI) $[M+H^+]^+ = 404.4$.

Example 28: Synthesis of [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine P-0231

[0245] [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0231** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** as shown in Scheme 184.

Scheme 184



Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (595):

[0246] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (**592**, 50.0 mg, 0.11 mmol, prepared as described in Example 27, Scheme 183) in ethanol (1.60 mL) and acetic acid (0.08 mL) were added 5-fluoro-pyridine-3-carbaldehyde (**594**, 43 mg, 0.34 mmol) and silica supported cyanoborohydride (1.21 mmol/g, 0.180 g). The reaction was irradiated with microwave on 300 watts, 100°C for 7 minutes. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the desired compound (**595**, 0.030 g, 48%).

Step 2 – Synthesis of [4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (P-0231):

[0247] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**595**, 0.030 g, 0.055 mmol) in tetrahydrofuran (6.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.034 g, 0.11 mmol) under an atmosphere of nitrogen. 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 anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0231**, 1.5 mg,

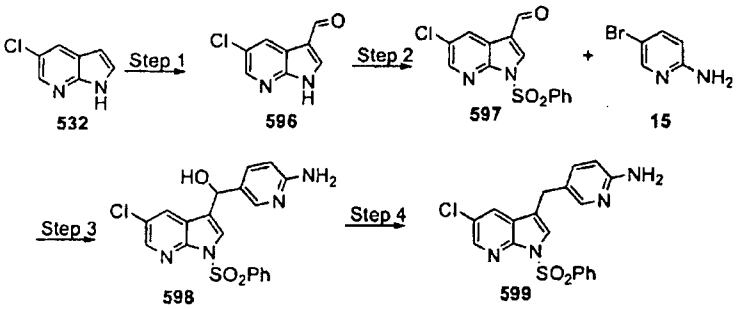
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6.7%). MS (ESI) $[M+H^+]^+ = 408.1$.

Example 29: Synthesis of 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine 599

[0248] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** was synthesized in 4 steps from 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** as shown in Scheme 185.

Scheme 185



Step 1 – Synthesis of 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (596):

[0249] To 5-chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 10.0 g, 65.5 mmol) in acetic acid (28.3 mL) were added hexamethylenetetramine (11.9 g, 85.2 mmol) and water (56.7 mL). The reaction was refluxed overnight, followed by addition of 200 mL of water. After 30 minutes, the reaction was filtered to recover the solid, then dried under air to give the desired compound (**596**, 7.0 g. 59%).

Step 2 – Synthesis of 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (597):

[0250] To 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**596**, 3.60 g, 0.0199 mol) in dichloromethane (100 mL) were added a solution of potassium hydroxide (9 M in water, 50 mL), tetrabutylammonium hydrogen sulfate (400 mg, 0.001 mol) and benzenesulfonyl chloride (2.9 mL, 0.023 mol). 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 anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate to give a white solid (**597**, 2.3 g, 36.0%).

Step 3 – Synthesis of (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (598):

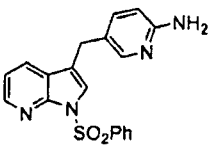
[0251] To 2-amino-5-bromopyridine (**15**, 3.10 g, 17.9 mmol) in tetrahydrofuran (80.0 mL) under

an atmosphere of nitrogen at -78 °C, a solution n-butyllithium (2.50 M in hexane, 7.10 mL) was added slowly. After 30 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (3.90 g dissolved in tetrahydrofuran 20.0 mL, 18.1 mmol) was added to the reaction mixture slowly, and then allowed to warm to room temperature for 1 hour. The reaction was cooled to -78 °C followed by adding a solution of n-butyllithium (2.50 M in Hexane, 7.10 mL). The reaction mixture was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature for 60 minutes. The reaction mixture was cooled to -78 °C, followed by adding a solution of n-butyllithium (2.50 M in Hexane, 7.50 mL) slowly. After 60 minutes, 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**597**, 1.90 g in 30 mL tetrahydrofuran, 5.92 mmol) was added to the reaction mixture. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature for 1 hour. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 20% methanol in dichloromethane to give the desired compound (**598**, 1.25 g, 50.9%). MS (ESI) $[M+H^+]^+ = 415.2$.

Step 4 – Synthesis of 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (599):

[0252] To (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**598**, 1.00 g, 0.00241 mol) in dichloromethane (25.0 mL) were added triethylsilane (3.00 mL, 0.0188 mol) and trifluoroacetic acid (1.50 mL, 0.0195 mol). The reaction was stirred at room temperature overnight, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**599**, 0.70 g, 73%).

[0253] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600**



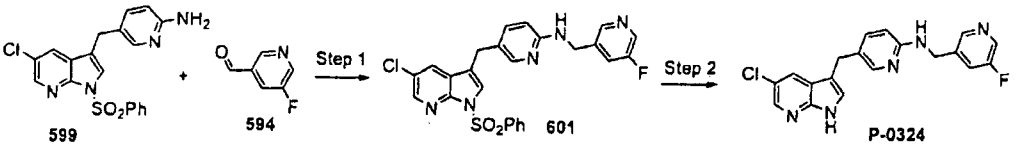
was prepared following the protocol of Scheme 185, substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 1H-pyrrolo[2,3-b]pyridine in Step 1. MS (ESI) $[M+H^+]^+ = 365.2$.

Example 30: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine P-0324

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[0254] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0324** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** as shown in Scheme 186.

Scheme 186



Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (601):

[0255] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**599**, 80.0 mg, 0.20 mmol, prepared as described in Example 29, Scheme 185) in ethanol (2.0 mL) and acetic acid (0.10 mL, 0.0018 mol) were added 5-fluoro-pyridine-3-carbaldehyde (**594**, 62.7 mg, 0.50 mmol) and sodium cyanoborohydride on silica gel (1.200 mmol/g loading; 0.251 g, 0.30 mmol). The reaction was irradiated with microwave on 300 watts, 100 °C for 10 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**601**, 0.060 g, 59%).

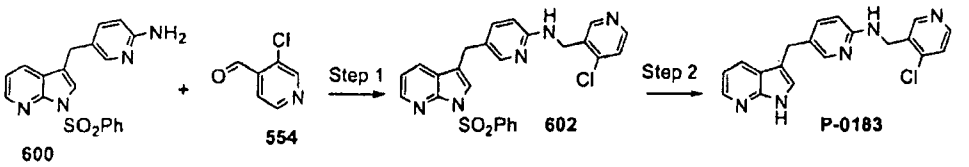
Step 2 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (P-0324):

[0256] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**601**, 0.060 g, 0.12 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.11 g, 0.35 mmol). The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0324**, 13.5mg, 31%). MS (ESI) $[M+H^+]^+ = 368.0$.

Example 31: Synthesis of (3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0183

[0257] (3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0183** was synthesized in 2 steps from 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 187.

Scheme 187



Step 1 – Synthesis of [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-pyridin-3-ylmethyl)-amine (602):

[0258] To 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 120.0 mg, 0.33 mmol, prepared as described in Example 29, Scheme 185) in acetonitrile (10.0 mL) were added 3-chloro-pyridine-4-carbaldehyde (**554**, 51.3 mg, 0.36 mmol), trifluoroacetic acid (0.30 mL, 0.0039 mol) and triethylsilane (0.60 mL, 0.0038 mol). The reaction was heated to reflux overnight, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% to 100% ethyl acetate in hexane to give the desired compound (**602**, 80 mg, 49.6%). MS $[M+H^+]^+ = 490.2$.

Step 2 – Synthesis of (3-chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0183):

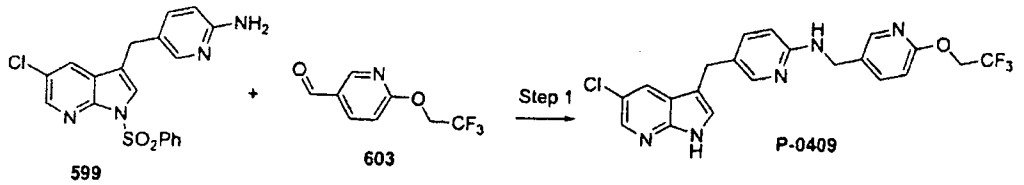
[0259] To [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-pyridin-3-ylmethyl)-amine (**602**, 0.08 g, 0.16 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.240 g, 0.76 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow solid (**P-0183**, 4.0 mg, 7%). MS (ESI) $[M+H^+]^+ = 350.2$.

Example 32: Synthesis of [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

[0260] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0409** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** as shown in Scheme 188.

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Scheme 188



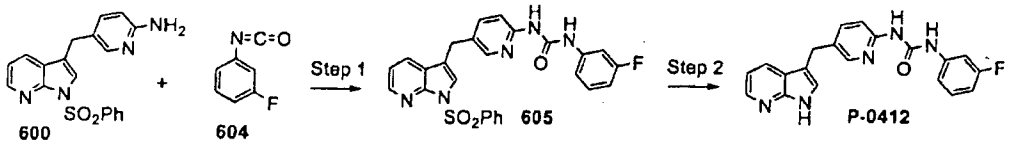
*Step 1 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-0409**):*

[0261] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**599**, 124.1 mg, 0.31 mmol, prepared as described in Example 29, Scheme 185) in ethanol (3.00 mL) and acetic acid (0.2 mL) were added 6-(2,2,2-trifluoro-ethoxy)-pyridine-3-carbaldehyde (**603**, 164.0 mg, 0.80 mmol) and silica supported cyanoborohydride (1.21 mmol/g, 0.700 g). The reaction was irradiated with microwave on 300 watts, 100°C for 150 minutes. To the reaction was added a solution of potassium hydroxide (9.0 M in water, 1.0 mL). The reaction was irradiated with microwave on 300 watts, 100 °C for 10 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0409**, 10.6 mg, 7.6%). MS ESI $[M+H^+]^+ = 448.4$.

Example 33: Synthesis of 1-(3-fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea P-0412

[0262] 1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea **P-0412** was synthesized in 2 steps from 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 189.

Scheme 189



*Step 1 – Synthesis of 1-[5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-(3-fluoro-phenyl)-urea (**605**):*

[0263] To 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 150.0 mg, 0.41 mmol, prepared as described in Example 29, Scheme 185) in acetonitrile (12.5 mL) were added 3-fluoro-isocyanato-benzene (**604**, 61.6 mg, 0.45 mmol), 4-dimethylaminopyridine (10.0 mg, 0.082 mmol) and triethylamine (0.25 mL, 0.0018 mol). The reaction mixture was heated at 70 °C overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**605**, 0.100 g, 48.4%).

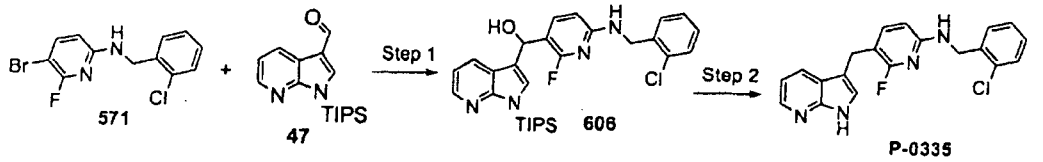
Step 2 – Synthesis of 1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea (P-0412):

[0264] To 1-[5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-(3-fluoro-phenyl)-urea (**605**, 0.100 g, 0.20 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.240 g, 0.76 mmol). The reaction was stirred at room temperature for 5 hours, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0412**, 17.9 mg, 24.8%). MS (ESI) $[M+H^+]^+ = 362.2$.

Example 34: Synthesis of (2-chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0335

[0265] (2-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0335** was synthesized in 2 steps from (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine **571** as shown in Scheme 190.

Scheme 190



Step 1 – Synthesis of [6-(2-chloro-benzylamino)-2-fluoro-pyridin-3-yl]-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (606):

[0266] To (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine (**571**, 0.635 g, 2.01 mmol, prepared as described in Example 21, Scheme 177) in tetrahydrofuran (25.0 mL) under an

atmosphere of nitrogen at -78 °C, a solution of n-butyllithium (2.50 M in hexane, 0.80 mL) was added slowly. After 20 minutes, tert-butyllithium (1.7 M in hexane, 2.40 mL) was added to the reaction and after 30 minutes, 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**47**, 0.575 g, 1.90 mmol) in tetrahydrofuran (8.0 mL) was added to the reaction. The reaction mixture was stirred at -78 °C for 60 minutes, then allowed to warm to room temperature for another 10 minutes. The reaction mixture was poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**606**, 0.180 g, 17.6%). MS (ESI) $[M+H^+]^+ = 539.2$.

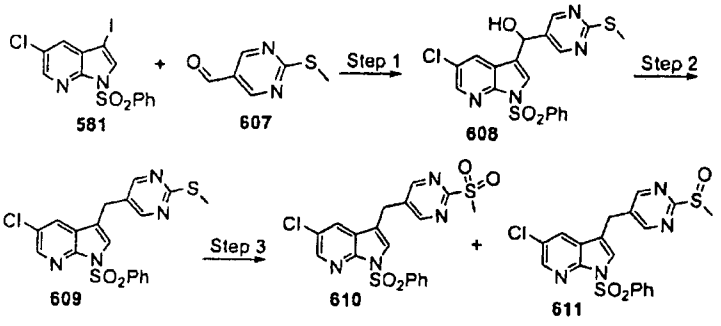
Step 2 – Synthesis of (2-chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0335):

[0267] To [6-(2-chloro-benzylamino)-2-fluoro-pyridin-3-yl]-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**606**, 180.0 mg, 0.33 mmol) in acetonitrile (15.0 mL) were added triethylsilane (1.00 mL, 6.26 mmol) and trifluoroacetic acid (0.50 mL, 6.50 mmol). The reaction was heated to reflux for 2 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0335**, 24.9 mg, 19.4%). MS (ESI) $[M+H^+]^+ = 367.0$.

Example 35: Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine 610

[0268] 1-Benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **610** was synthesized in 3 steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** as shown in Scheme 191.

Scheme 191



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Step 1 – Synthesis of (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (608):

[0269] To a solution of 1-Benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 4.36 g, 10.4 mmol) in tetrahydrofuran (100.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran. 5.06 mL) was added slowly. The reaction was allowed to warm to 5 °C over 60 minutes, then cooled to -40 °C, followed by adding 2-methylsulfanyl-pyrimidine-5-carbaldehyde (**607**, 1.30 g, 8.43 mmol, dissolved in tetrahydrofuran 15.0 mL). The reaction was allowed to warm to 10 °C over 2 hours. The reaction was poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give the desired compound (**608**, 3.00 g, 79.6%). MS (ESI) $[M+H^+]^+ = 447.2$.

Step 2 – Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (609):

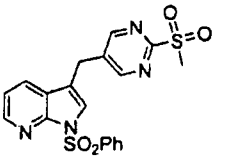
[0270] To (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**608**, 0.35 g, 0.78 mmol) in dichloromethane (15.0 mL) were added triethylsilane (2.00 mL, 12.52 mmol) and trifluoroacetic acid (1.00 mL, 13.0 mmol). The reaction was stirred at 35 °C overnight, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**609**, 0.25 g, 74%). MS (ESI) $[M+H^+]^+ = 430.9$.

Step 3 - Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (610) and 1-benzenesulfonyl-5-chloro-3-(2-methanesulfinyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (611):

[0271] To 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**609**, 0.500 g, 1.16 mmol) in dichloromethane (15.0 mL) was added meta-chloroperoxybenzoic acid (max. 77%, 0.572 g, 2.55 mmol) at 0 °C. The reaction was stirred at 0 °C for 70 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compounds (**610**, 0.310 g, 57.7%), MS (ESI) $[M+H^+]^+ = 463.1$; and (**611**, 0.200 g, 38.6%), MS (ESI) $[M+H^+]^+ = 447.2$.

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[0272] 1-Benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **612**

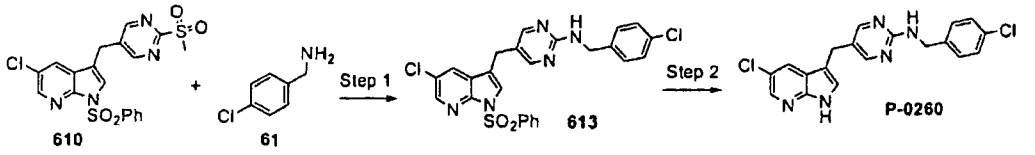


was prepared following the protocol of Scheme 191, substituting 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** with 1-benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine in Step 1.

Example 36: Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine P-0260

[0273] (4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-0260** was synthesized in 2 steps from 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **610** as shown in Scheme 192.

Scheme 192



*Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-chloro-benzyl)-amine (**613**):*

[0274] To 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**610**, 0.060 g, 0.13 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.80 mL) was added p-chlorobenzylamine (**61**, 0.20 g, 1.4 mmol). The reaction was irradiated with microwave on 300 watts, 150 °C for 15 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**613**, 0.05 g, 74%). MS (ESI) $[M+H^+]^+ = 524.3$.

*Step 2 – Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0260**):*

[0275] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-

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yl]-(4-chloro-benzyl)-amine (**613**, 0.050 g, 0.095 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.20 g, 0.63 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate in hexane to give an off-white solid (**P-0260**, 16.9 mg, 46%). MS (ESI) $[M+H^+]^+$ = 385.9.

[0276] Additional compounds were prepared following the protocol of Scheme 192, substituting p-chlorobenzylamine **61** with a suitable amine in Step 1. The following compounds were prepared following this protocol:

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,6-difluoro-benzyl)-amine (**P-0261**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0262**),

(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0263**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine (**P-0264**),

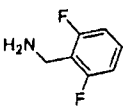
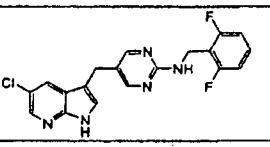
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine (**P-0265**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0266**),

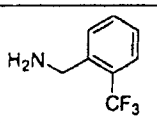
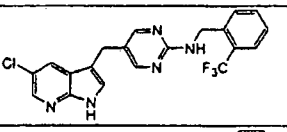
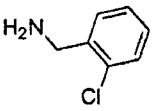
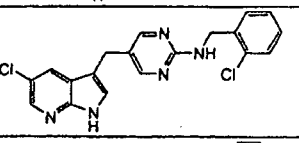
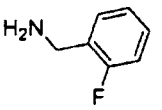
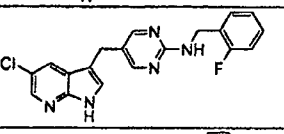
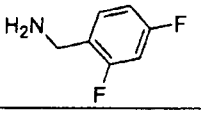
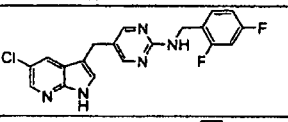
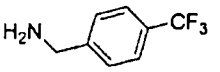
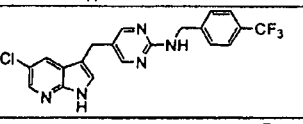
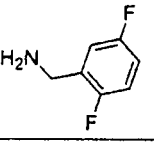
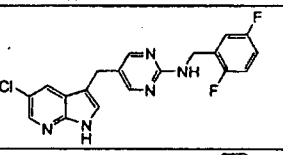
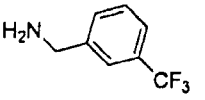
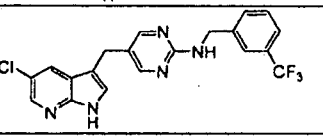
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine (**P-0267**), and

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine (**P-0268**).

The following table indicates the amine (Column 2) used in Scheme 192 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Amine in Step 1	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0261			384.1

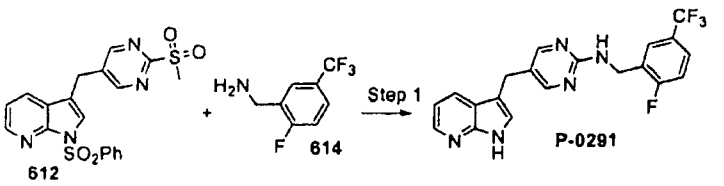
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P-0262			418.9
P-0263			384.2
P-0264			368.2
P-0265			386.2
P-0266			418.9
P-0267			$[M-H^+]^-$ = 384.0
P-0268			419.2

Example 37: Synthesis of (2-fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine P-0291

[0277] (2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-0291** was synthesized in 1 step from 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **612** as shown in Scheme 193.

Scheme 193



*Step 1 – Synthesis of (2-fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0291**):*

[0278] To 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**612**, 0.080 g, 0.19 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.00 mL) was added 2-fluoro-5-trifluoromethyl-benzylamine (**614**, 0.20 g, 1.0 mmol). The reaction was irradated with microwave on 300 watts, 150°C for 15 minutes. Potassium hydroxide in water (1.00 M, 2.00 mL) was added to the reaction. The reaction was irradiated with microwave on 300 watts, 90°C for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0291**, 37.4 mg, 50%). MS (ESI) $[M+H^+]^+$ = 402.6.

[0279] Additional compounds were prepared following the protocol of Scheme 193, substituting 2-fluoro-5-trifluoromethyl-benzylamine **614** with a suitable amine. The following compounds were prepared following this protocol:

(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0292**),

(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0293**),

(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0294**),

(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0295**),

(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0300**),

(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0301**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0302**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0303**),

(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0304**),

(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0305**),

(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0306**),

(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0307**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0308**),

(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

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amine (**P-0309**),

(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0310**),

(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0311**),

(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0312**),

(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0313**),

(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0314**),

(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0315**),

(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0316**),

(5-Chloro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0317**),

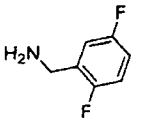
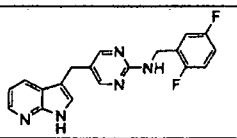
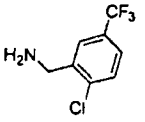
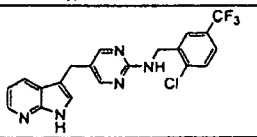
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0318**),

(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0319**),

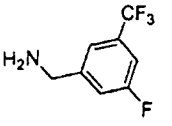
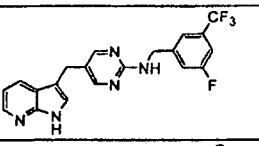
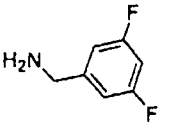
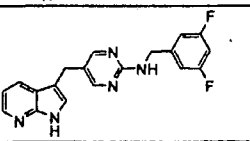
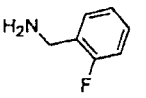
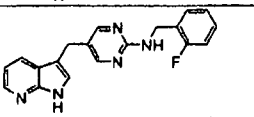
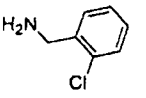
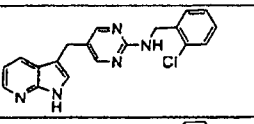
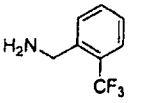
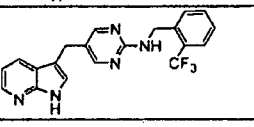
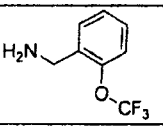
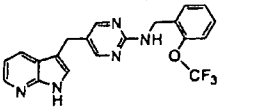
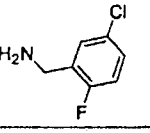
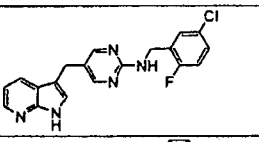
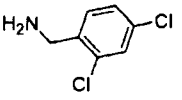
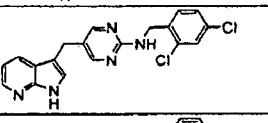
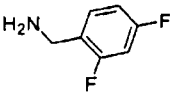
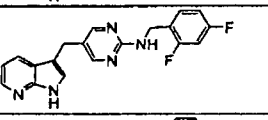
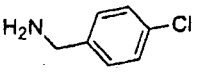
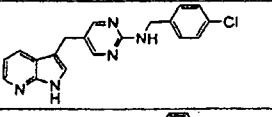
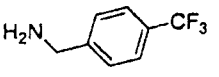
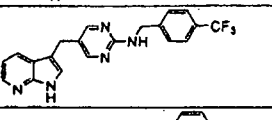
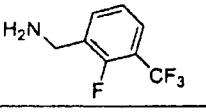
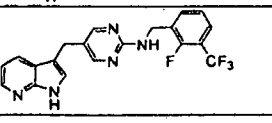
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0320**), and

(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0407**).

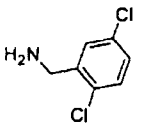
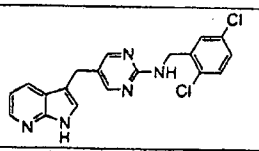
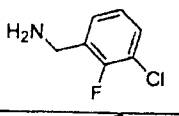
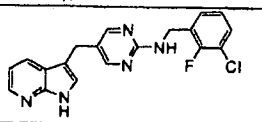
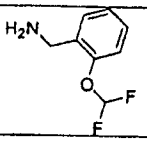
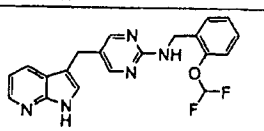
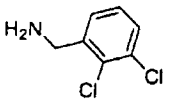
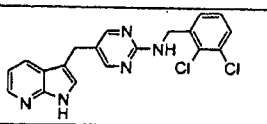
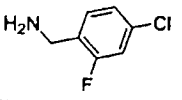
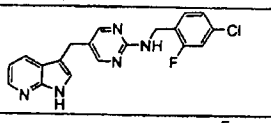
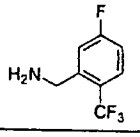
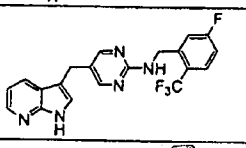
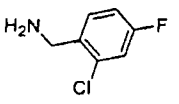
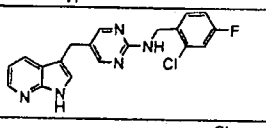
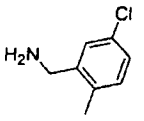
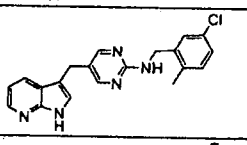
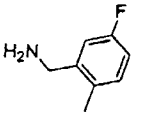
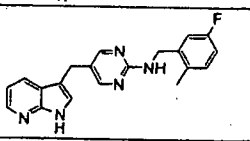
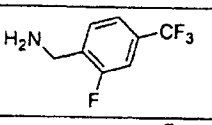
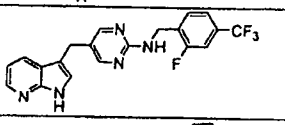
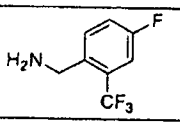
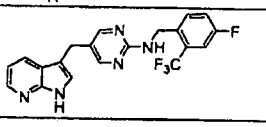
The following table indicates the amine (Column 2) used in Scheme 193 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

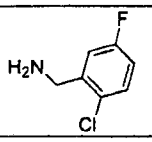
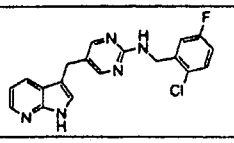
Compound number	Amine	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0292			352.3
P-0293			418.2

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P-0294			402.5
P-0295			352.3
P-0300			334.5
P-0301			349.9
P-0302			384.0
P-0303			400.5
P-0304			367.9
P-0305			383.9
P-0306			352.4
P-0307			352.0
P-0308			384.0
P-0309			402.5

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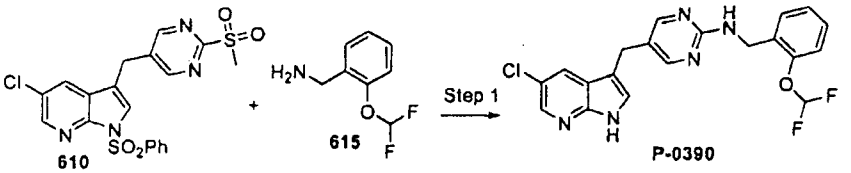
P-0310			389.0
P-0311			368.0
P-0312			382.5
P-0313			385.0
P-0314			367.9
P-0315			402.4
P-0316			368.2
P-0317			364.8
P-0318			348.6
P-0319			402.5
P-0320			402.5

P-0407			368.3

Example 38: Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine P-0390

[0280] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine **P-0390** was synthesized in 1 step from 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine 610 as shown in Scheme 194.

Scheme 194



Step 1 – Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine (P-0390)

[0281] To 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**610**, 0.060 g, 0.13 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.40 mL) was added 2-difluoromethoxy-benzylamine (**615**, 0.200 g, 1.16 mmol). The reaction was irradiated with microwave on 300 watts, 150 °C for 15 minutes. Potassium hydroxide in water (1.00 M, 2.00 mL) was added to the reaction. The reaction was irradiated with microwave on 300 watts, 90 °C for 10 minutes, then poured into ethyl acetate and water. The organic layer was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0390**, 10.9 mg, 20%). MS (ESI) $[M+H^+]^+ = 418.0$.

[0282] Additional compounds were prepared following the protocol of Scheme 194, substituting 2-difluoromethoxy-benzylamine **615** with a suitable amine. The following compounds were prepared following this protocol:

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-benzyl)-amine (**P-0289**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-trifluoromethyl-benzyl)-amine (**P-0391**),

(3-Chloro-2-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0392**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-3-trifluoromethyl-benzyl)-amine (**P-0393**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-4-trifluoromethyl-benzyl)-amine (**P-0394**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,3-difluoro-benzyl)-amine (**P-0395**),

(2-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0396**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0402**),

(2-Chloro-5-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0408**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine (**P-0416**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-pyrrolidin-1-yl-ethyl)-amine (**P-0417**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0418**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0419**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethoxy-benzyl)-amine (**P-0420**),

(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0421**),

[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]-(4-fluoro-benzyl)-amine (**P-0423**),

(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0424**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,5-difluoro-benzyl)-amine (**P-0425**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(2-fluoro-phenyl)-ethyl]-amine (**P-0426**),

[1-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

amine (**P-0427**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-0428**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0429**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0430**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methyl-benzyl)-amine (**P-0431**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-benzyl)-amine (**P-0433**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-ethyl)-amine (**P-0434**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexylmethyl-amine (**P-0435**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-0436**),
[2-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0437**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-difluoromethoxy-benzyl)-amine (**P-0438**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methoxy-benzyl)-amine (**P-0439**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-benzyl)-amine (**P-0440**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-ethyl)-amine (**P-0441**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-benzyl)-amine (**P-0442**),
(3-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0443**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-ethoxy-benzyl)-amine (**P-0444**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-morpholin-4-yl-benzyl)-amine (**P-0445**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-difluoromethoxy-benzyl)-

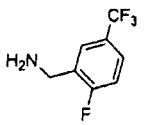
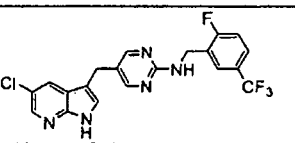
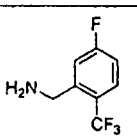
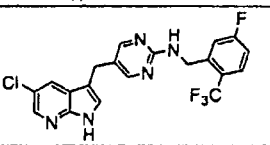
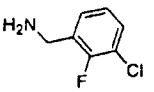
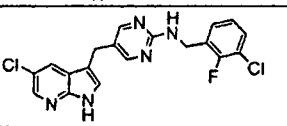
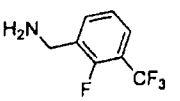
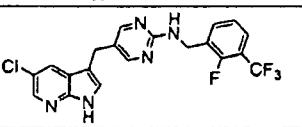
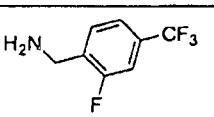
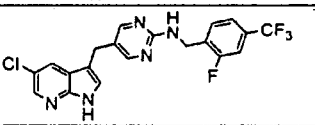
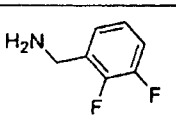
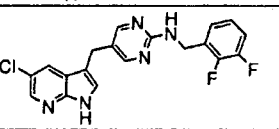
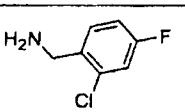
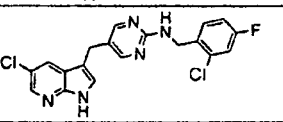
amine (**P-0446**),

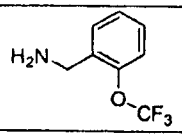
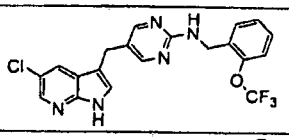
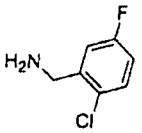
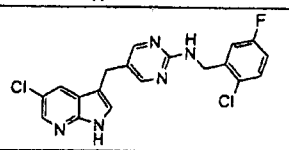
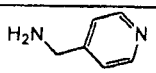
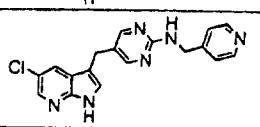
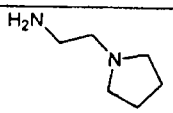
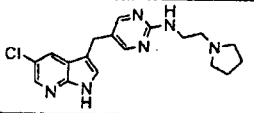
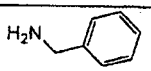
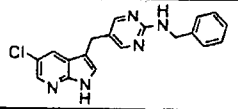
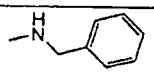
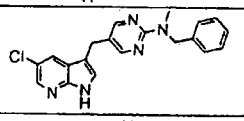
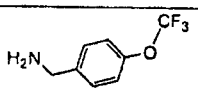
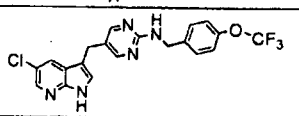
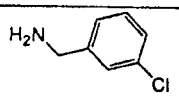
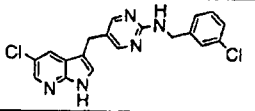
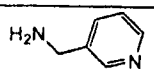
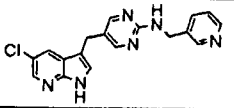
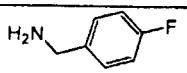
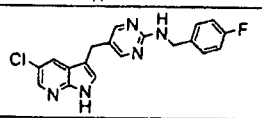
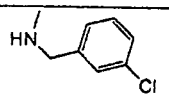
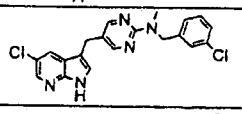
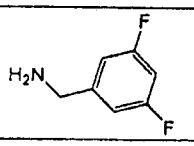
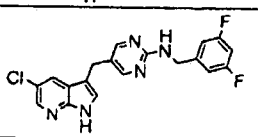
(4-Chloro-3-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0447**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(3-fluoro-phenyl)-ethyl]-amine (**P-0448**), and

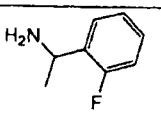
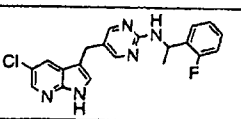
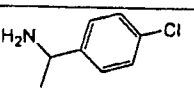
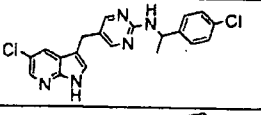
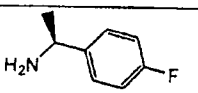
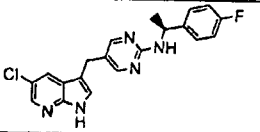
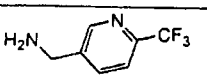
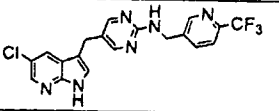
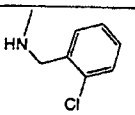
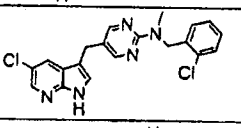
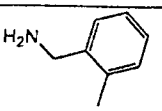
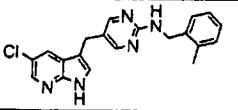
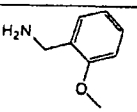
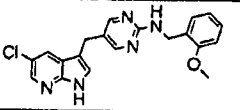
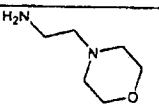
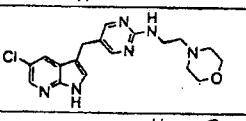
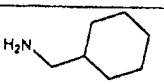
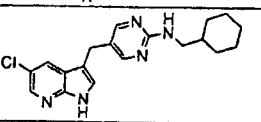
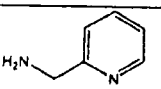
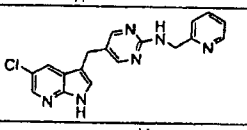
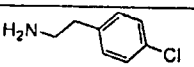
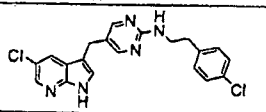
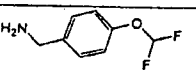
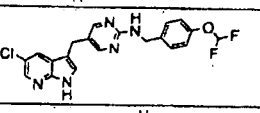
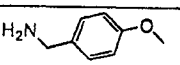
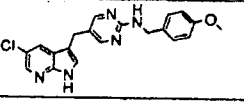
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-dimethylamino-benzyl)-amine (**P-0449**).

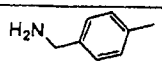
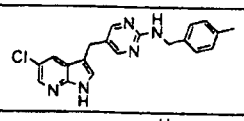
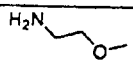
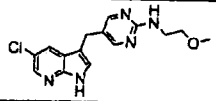
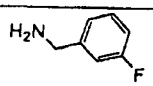
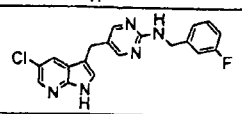
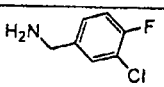
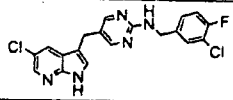
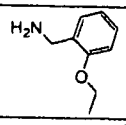
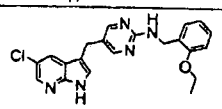
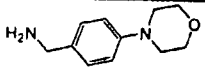
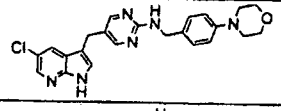
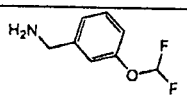
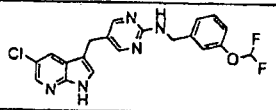
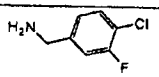
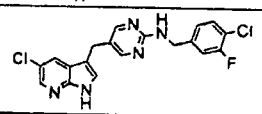
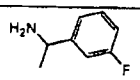
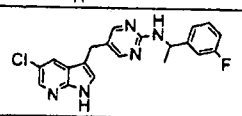
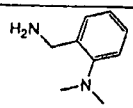
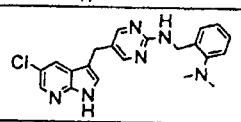
The following table indicates the amine (Column 2) used in Scheme 194 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Amine	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0289			436.0
P-0391			436.0
P-0392			402.0
P-0393			$[M-H^+]^-$ = 434.1
P-0394			437.3
P-0395			386.0
P-0396			402.0

P-0402			434.3
P-0408			402.0
P-0416			351.1
P-0417			357.1
P-0418			350.3
P-0419			364.3
P-0420			434.3
P-0421			383.9
P-0422			351.1
P-0423			368.3
P-0424			398.3
P-0425			386.3

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P-0426			382.3
P-0427			398.3
P-0428			382.3
P-0429			419.1
P-0430			397.9
P-0431			364.3
P-0433			380.3
P-0434			373.1
P-0435			356.3
P-0436			351.1
P-0437			397.9
P-0438			416.3
P-0439			380.3

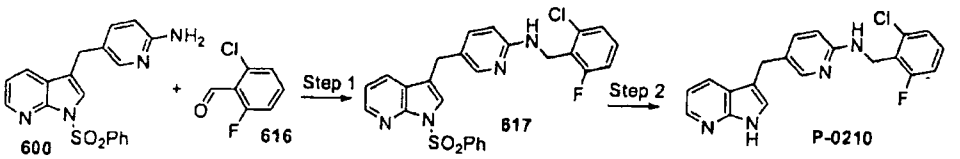
P-0440			364.3
P-0441			317.9
P-0442			368.3
P-0443			401.9
P-0444			393.9
P-0445			435.1
P-0446			416.3
P-0447			402.3
P-0448			382.3
P-0449			393.1

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Example 39: Synthesis of (2-chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0210

[0283] (2-Chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0210** was synthesized in 2 steps from 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 195.

Scheme 195



Step 1 – Preparation of [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-chloro-6-fluoro-benzyl)-amine (617):

[0284] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 30 mg, 0.083 mmol, prepared as described in Example 29, Scheme 185) was combined with 2-chloro-6-fluoro-benzaldehyde (**616**, 26.2 mg, 0.165 mmol) in a 2 mL microwave reaction vial. The mixture was dissolved in ethanol:acetic acid (95:5, 0.6 mL). Silica supported cyanoborohydride (1.0 mmol/g, 83 mg, 0.083 mmol) was added and the mixture was irradiated with microwave on 300 watts for 5 minutes at 100 °C. The silica was separated by centrifuging and the supernatant solution was decanted. The silica residue was rinsed with ethanol (0.500 mL) and centrifuged. The solvents were combined and removed under reduced pressure to give compound **617**, which was used in the next step without further purification.

*Step 2 – Preparation of (2-chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0210**):*

[0285] [5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-chloro-6-fluoro-benzyl)-amine **617** was combined with methanol:potassium hydroxide (1M) (1:1, 0.5 mL). The mixture was heated at 80 °C for 2 hours. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in dimethylsulfoxide (0.4 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID) eluting with 0.1 % trifluoroacetic acid in water and 20-100 % acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0210**. MS (ESI) $[M+H^+]^+ = 367.1$.

[0286] Additional compounds were prepared following the protocol of Scheme 195, replacing 2-chloro-6-fluoro-benzaldehyde **616** with an appropriate aldehyde in Step 1. The following compounds were made following this procedure:

Phenethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0211**),

(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0212**),

(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0213**),

(3-Bromo-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0214**),

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

(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0216**),

(2-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0217**),

(1-Methyl-1H-benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0218**),

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

(1H-Benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0220**),

(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0221**),

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

(3-Fluoro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0223**),

(6-Methoxy-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0224**),

(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0225**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0226**),

(3,5-Dichloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0227**),

(6-Morpholin-4-yl-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0228**),

(3-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0229**),

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

(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0342**),

(3-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0343**),

(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0344**),

(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0345**),

(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0346**),

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

(4-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0348**),

(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0349**),

(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0350**),

(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0351**),

(2-Fluoro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0352**),

Dimethyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine (**P-0353**),

(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0354**),

(5-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0355**),

(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0356**),

(2-Propoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0357**),

(2-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0358**),

(2-Chloro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0359**),

(2-Fluoro-6-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0360**),

[2-(2-Morpholin-4-yl-ethoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-

amine (**P-0361**),

(2,3-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0362**),

(2-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0363**),

(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0364**),

(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0365**),

(5-Fluoro-2-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0366**),

(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0367**),

(2-Fluoro-4-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0368**),

[2-(3-Dimethylamino-propoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0369**),

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

(2-Fluoro-5-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0371**),

(4-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0372**),

(3-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0373**),

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

(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0375**),

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

Propane-1-sulfonic acid (2-fluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-0377**),

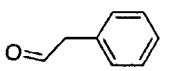
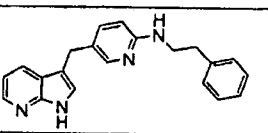
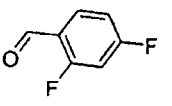
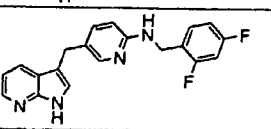
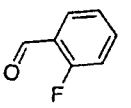
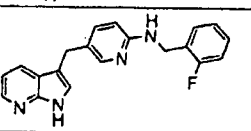
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0380**),

Pyrimidin-5-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0381**),

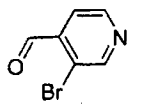
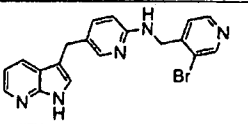
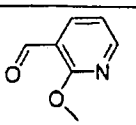
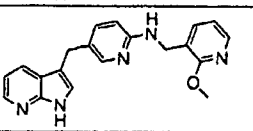
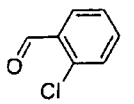
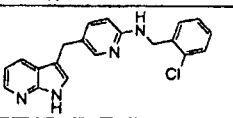
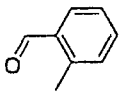
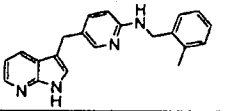
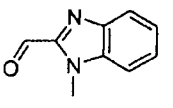
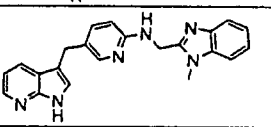
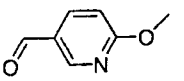
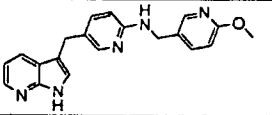
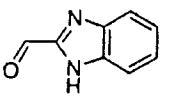
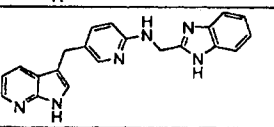
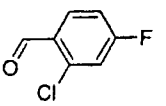
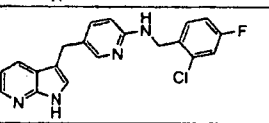
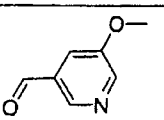
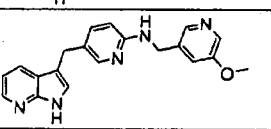
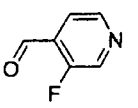
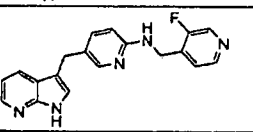
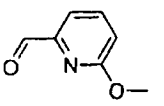
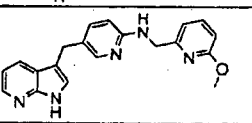
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0382**),

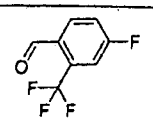
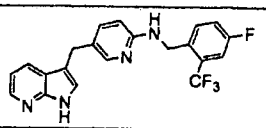
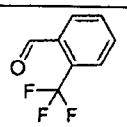
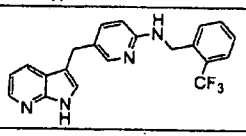
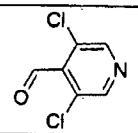
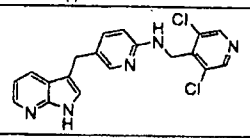
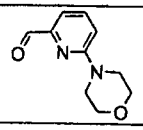
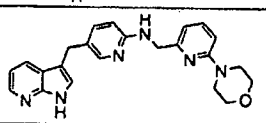
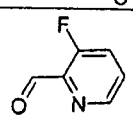
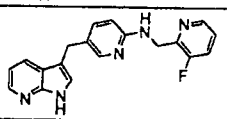
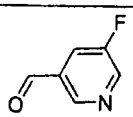
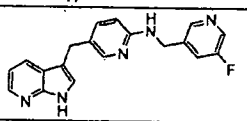
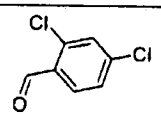
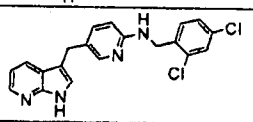
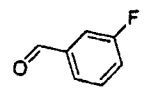
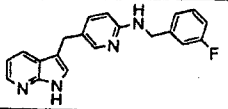
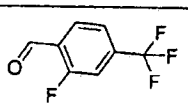
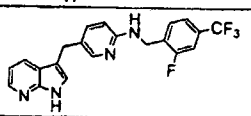
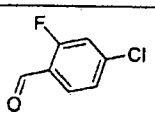
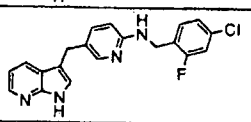
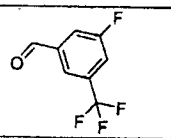
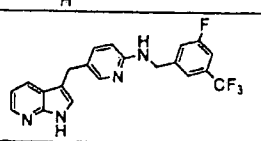
(2-Ethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0383**),
2,2-Dimethyl-N-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-propionamide (**P-0384**),
Methyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine (**P-0385**),
Methyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine (**P-0386**),
(2-Chloro-4-methanesulfonyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0387**),
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0397**),
(2,2-Difluoro-benzo[1,3]dioxol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0398**),
Dimethyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine (**P-0399**),
(5-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0400**), and
(2-Methoxy-pyrimidin-5-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0401**).

The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 195 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

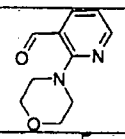
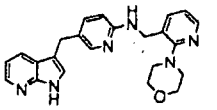
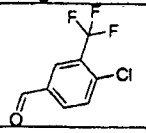
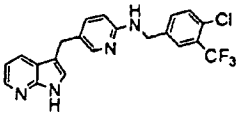
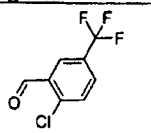
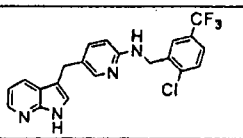
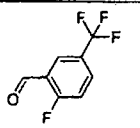
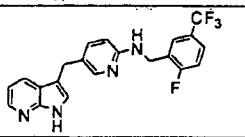
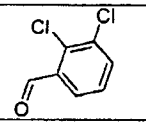
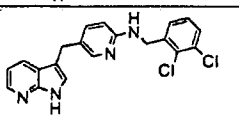
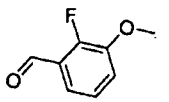
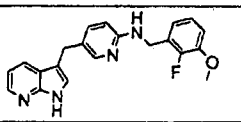
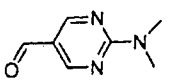
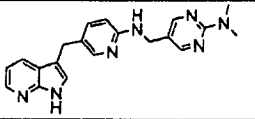
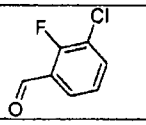
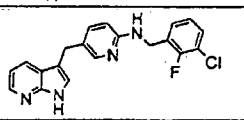
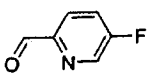
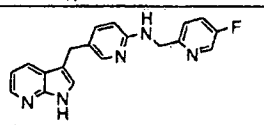
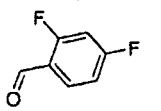
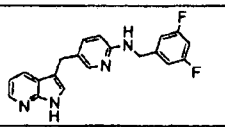
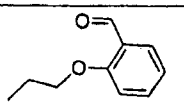
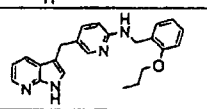
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0211			329.1
P-0212			351.1
P-0213			338.1

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Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0214			395.9
P-0215			345.9
P-0216			349.1
P-0217			329.1
P-0218			369.1
P-0219			345.9
P-0220			355.1
P-0221			367.1
P-0222			345.9
P-0223			334.3
P-0224			345.9

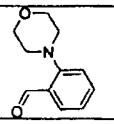
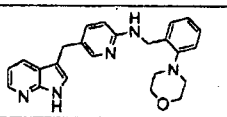
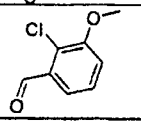
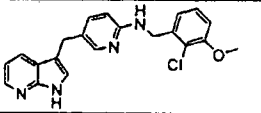
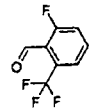
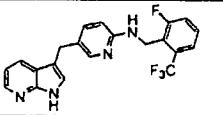
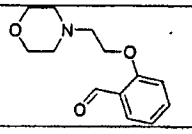
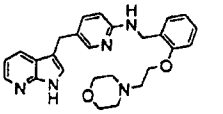
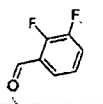
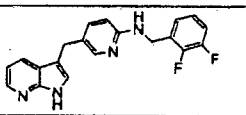
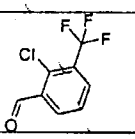
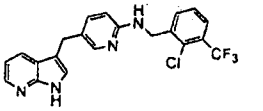
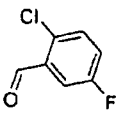
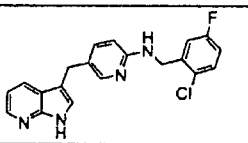
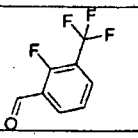
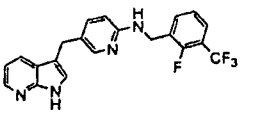
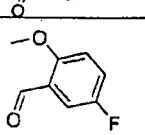
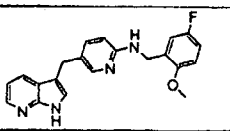
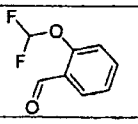
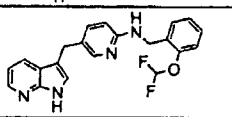
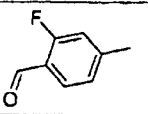
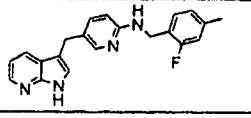
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0225			401.1
P-0226			383.1
P-0227			383.9
P-0228			401.1
P-0229			334.3
P-0230			334.3
P-0342			383.1
P-0343			333.1
P-0344			401.1
P-0345			367.1
P-0346			401.1

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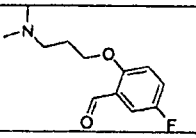
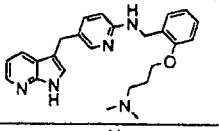
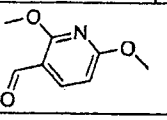
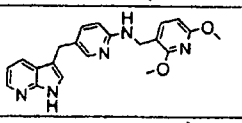
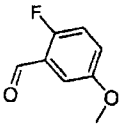
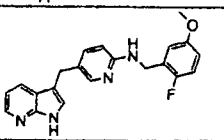
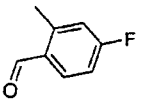
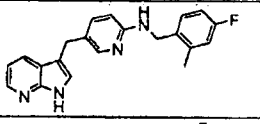
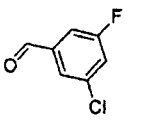
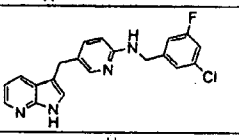
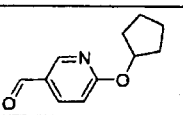
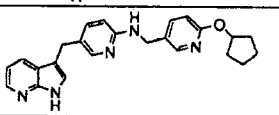
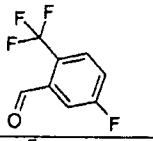
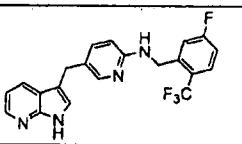
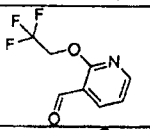
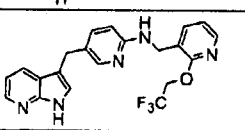
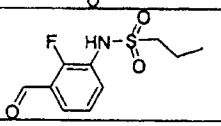
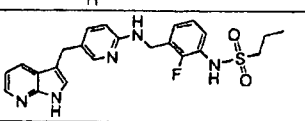
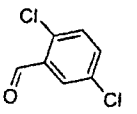
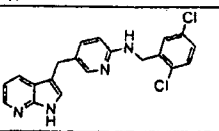
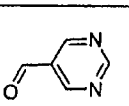
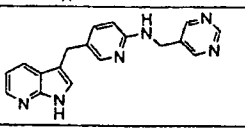
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0347			401.1
P-0348			417.1
P-0349			417.1
P-0350			401.1
P-0351			383.1
P-0352			363.1
P-0353			360.3
P-0354			367.1
P-0355			334.3
P-0356			351.1
P-0357			373.1

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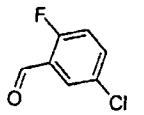
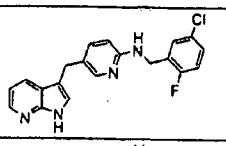
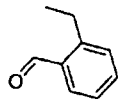
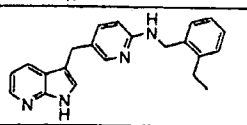
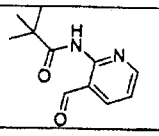
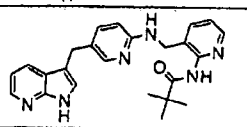
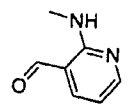
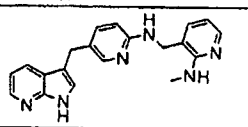
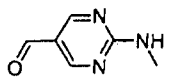
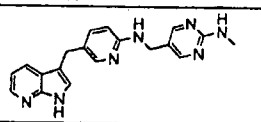
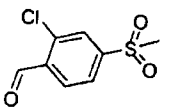
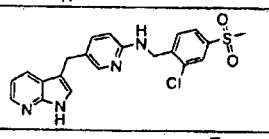
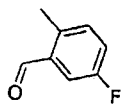
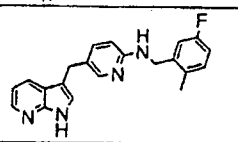
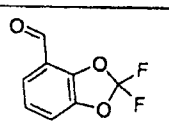
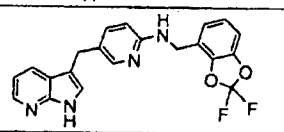
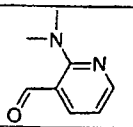
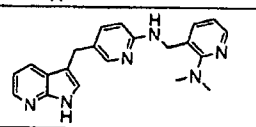
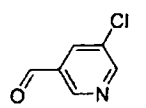
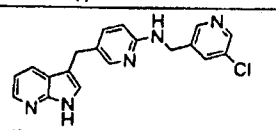
T2
S26109

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0358			400.3
P-0359			379.1
P-0360			401.1
P-0361			444.3
P-0362			351.1
P-0363			417.1
P-0364			367.1
P-0365			401.1
P-0366			363.1
P-0367			381.1
P-0368			347.1

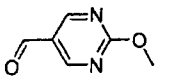
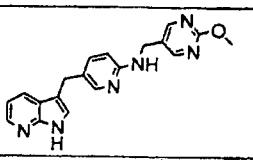
162

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0369			416.3
P-0370			376.3
P-0371			363.1
P-0372			347.1
P-0373			367.1
P-0374			400.3
P-0375			401.1
P-0376			413.9
P-0377			453.9
P0380			383.1
P-0381			317.2

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Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0382			367.1
P-0383			343.1
P-0384			415.2
P-0385			345.4
P-0386			345.2
P-0387			427.1
P-0397			347.1
P-0398			396.1
P-0399			359.1
P-0400			350.3

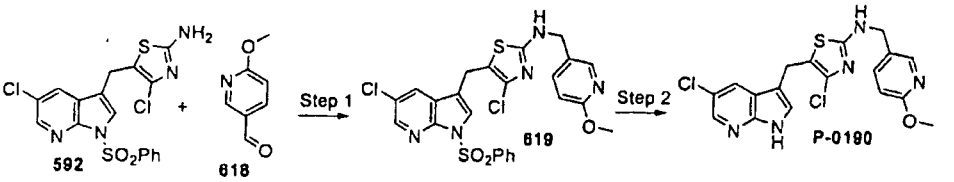
169

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0401			347.1

Example 40: Synthesis of [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine P-0190

[0287] [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine P-0190 was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** as shown in Scheme 196.

Scheme 196



*Step I – Preparation of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**619**):*

[0288] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (**592**, 30 mg, 0.083 mmol, prepared as described in Example 27, Scheme 183) was combined with 6-methoxy-pyridine-3-carbaldehyde (**618**, 26.2 mg, 0.165 mmol) in a 2 mL microwave reaction vial. The mixture was dissolved in ethanol: acetic acid (95:5, 0.6 mL). Silica supported cyanoborohydride (1.0 mmol/g, 83 mg, 0.083 mmol) was added and the mixture was irradiated with microwave on 300 watts for 5 minutes at 100 °C. The silica was separated by centrifuging and the supernatant solution was decanted. The silica residue was rinsed with ethanol (0.500 mL) and centrifuged. The solvents were combined and removed under reduced pressure to give the desired compound **619**, which was used without further purification.

*Step II – Preparation of [4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0190**):*

[0289] [5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **619** was combined with methanol: potassium hydroxide (1M) (1:1, 0.5 mL). The mixture was heated at 80 °C for 2 hours. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in dimethylsulfoxide (0.4 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID) eluting with 0.1 % trifluoroacetic acid in water and 20-100 % acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0190**. MS (ESI) $[M+H^+]^+ = 419.9$.

[0290] Additional compounds were prepared following the protocol of Scheme 196, replacing 6-methoxy-pyridine-3-carbaldehyde **618** with a suitable aldehyde in Step 1. The following compounds were made following this procedure:

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-thiazol-2-ylmethyl-amine (**P-0189**),

Benzyl-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0192**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine (**P-0193**),

(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0194**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0195**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine (**P-0196**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine (**P-0197**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-2H-pyrazol-3-ylmethyl)-amine (**P-0198**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine (**P-0199**),

[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]-(2-methyl-thiazol-4-ylmethyl)-amine (**P-0201**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-methyl-thiazol-5-ylmethyl)-amine (**P-0202**),

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

ylmethyl)-amine (**P-0203**),

[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]-pyridin-4-ylmethyl-amine (**P-0237**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-chloro-pyridin-4-ylmethyl)-amine (**P-0238**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1-ethyl-1H-pyrazol-4-ylmethyl)-amine (**P-0239**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0240**),

[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-chloro-6-fluoro-benzyl)-amine (**P-0243**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-phenethyl-amine (**P-0244**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-difluoro-benzyl)-amine (**P-0245**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-fluoro-benzyl)-amine (**P-0246**),

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

(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0248**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine (**P-0249**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine (**P-0250**),

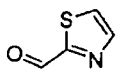
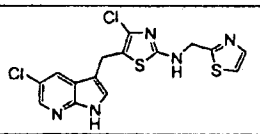
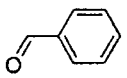
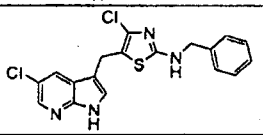
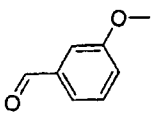
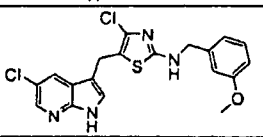
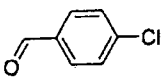
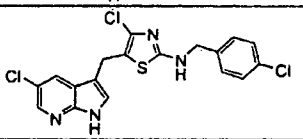
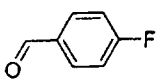
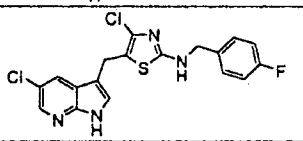
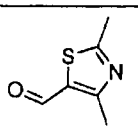
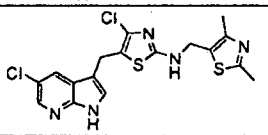
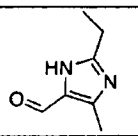
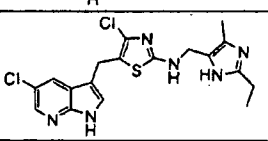
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-2-ylmethyl)-amine (**P-0251**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-0252**),

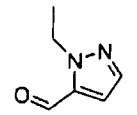
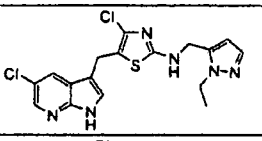
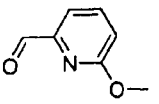
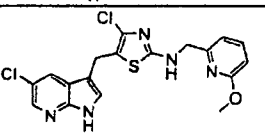
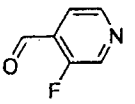
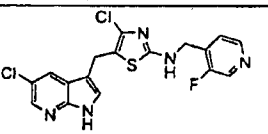
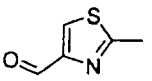
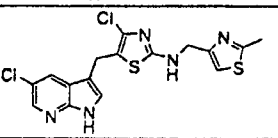
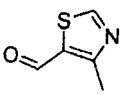
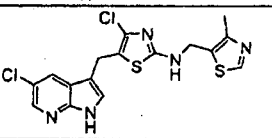
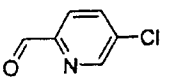
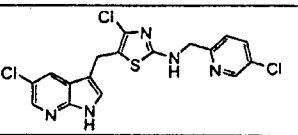
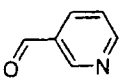
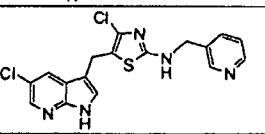
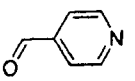
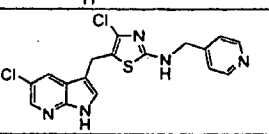
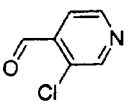
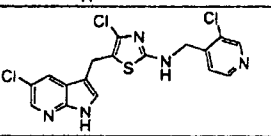
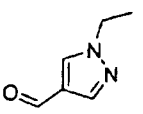
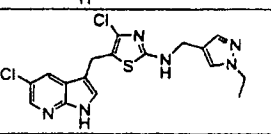
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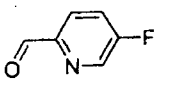
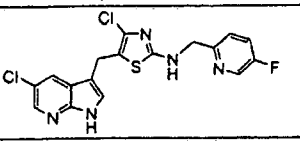
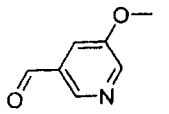
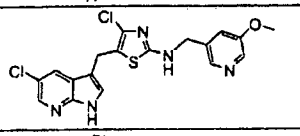
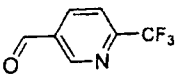
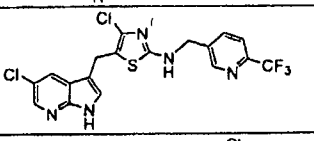
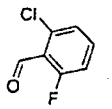
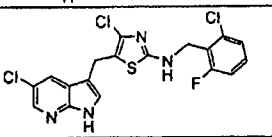
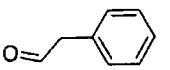
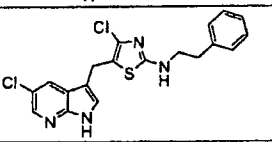
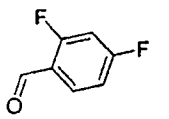
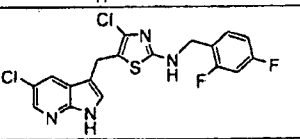
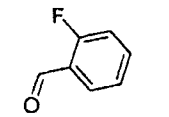
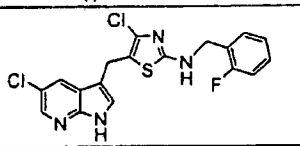
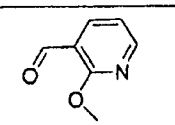
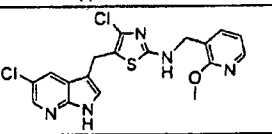
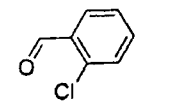
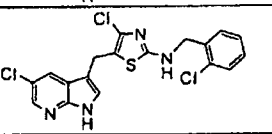
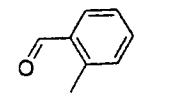
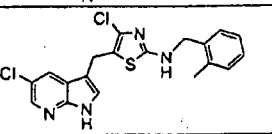
ylmethyl)-amine (**P-0253**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0254**), and
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine (**P-0255**).

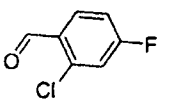
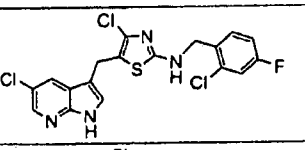
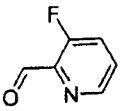
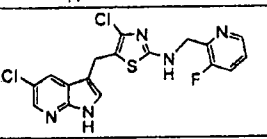
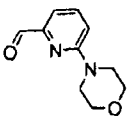
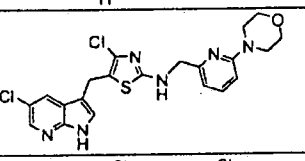
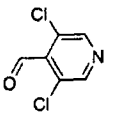
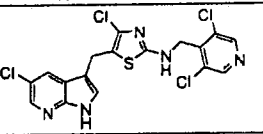
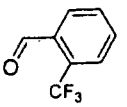
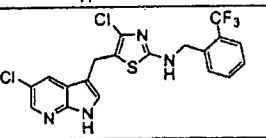
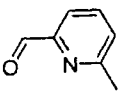
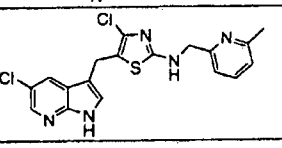
The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 196 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0189			395.9
P-0192			389.1
P-0193			419.1
P-0194			425.1
P-0195			407.1
P-0196			423.9
P-0197			421.1

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Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0198			407.1
P-0199			419.9
P-0200			407.9
P-0201			409.9
P-0202			409.9
P-0203			423.9
P-0236			390.3
P-0237			390.3
P-0238			425.9
P-0239			407.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0240			407.9
P-0241			419.9
P-0242			458.3
P-0243			443.1
P-0244			403.1
P-0245			424.7
P-0246			407.1
P-0247			419.9
P-0248			424.7
P-0249			403.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0250			441.1
P-0251			407.9
P-0252			475.1
P-0253			459.9
P-0254			457.1
P-0255			404.3

[0291] Additional compounds were prepared following the protocol of Scheme 196, replacing 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** with 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **593** (prepared as described in Example 27, Scheme 183) in addition to replacing 6-methoxy-pyridine-3-carbaldehyde **618** with a suitable aldehyde in Step 1. The following compounds were made following this procedure:

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine (**P-0204**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine (**P-0205**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0206**),

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

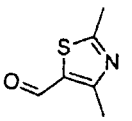
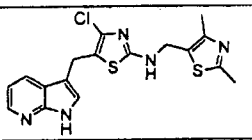
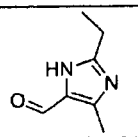
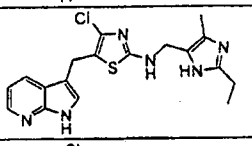
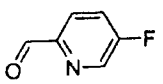
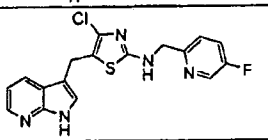
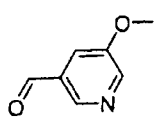
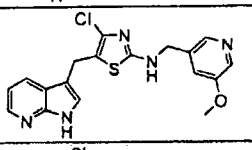
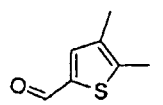
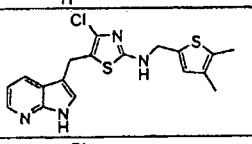
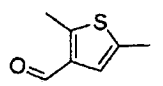
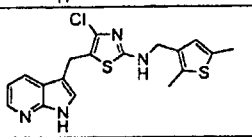
176

amine (**P-0207**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4,5-dimethyl-thiophen-2-ylmethyl)-amine (**P-0208**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-thiophen-3-ylmethyl)-amine (**P-0209**),

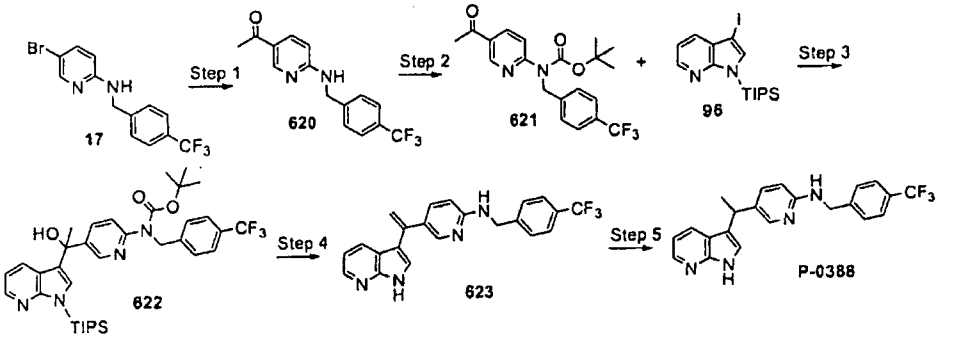
The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 196 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0204			390.3
P-0205			387.1
P-0206			373.9
P-0207			386.3
P-0208			389.1
P-0209			389.1

Example 41: Synthesis of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine P-0388

[0292] 5-[1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine **P-0388** was synthesized from (5-bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine **17** as shown in Scheme 197.

Scheme 197



Step 1 - Preparation of 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-ethanone (620):

[0293] (5-Bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (**17**, 3.00 g, 9.06 mmol) was dissolved in tetrahydrofuran (80 mL). The reaction was cooled at -78 °C under an atmosphere of argon. 2.5 M n-butyllithium in hexane (10.9 mL) was added. The reaction was stirred at -78 °C for 60 minutes. N-Methoxy-N-methylacetamide (1.93 mL, 18.1 mmol) was added to the reaction, which was allowed to warm to room temperature. The reaction was poured into 1M ammonium chloride and brine and extracted with ethyl acetate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (ethyl acetate:hexanes) to provide the desired compound as an oil that crystallized to a white solid (**620**, 1.328 g, 50%), consistent with the compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=295.3.

Step 2 - Preparation of (5-acetyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (621):

[0294] To 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-ethanone (**620**, 1.30 g, 4.42 mmol) in tetrahydrofuran (15.0 mL) were added di-tert-butyldicarbonate (1.10 g, 5.04 mmol), 4-dimethylaminopyridine (0.0259 g, 0.21 mmol) and N,N-diisopropylethylamine (0.888 mL, 5.10 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3 days.

The mixture was extracted with ethyl acetate and saturated sodium bicabonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (0-15% ethyl acetate:hexanes) to provide the desired compound as an oil that solidified to a white solid (**621**, 1.29g, 74%), consistent with the compound structure by ^{1}H-NMR.

Step 3 - Preparation of 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-1-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanol (622):

[0295] 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 485.9 mg, 1.21 mmol) was dissolved in tetrahydrofuran (8 mL) at -20 °C under an atmosphere of nitrogen. 2.0 M isopropylmagnesium chloride in tetrahydrofuran (0.655 mL) was added. The reaction was stirred at -20 °C for 1 hour. Into the reaction was added (5-acetyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**621**, 300.0 mg, 0.76 mmol) in tetrahydrofuran (6 mL) The reaction was allowed to warm to room temperature overnight. The mixture was extracted with ethyl acetate and saturated sodium bicabonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography on the (ethyl acetate:hexanes), to provide the desired compound as an oil (**622**, 125 mg, 29%), consistent with the compound structure by ^{1}H-NMR.

Step 4 - Preparation of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-vinyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (623):

[0296] 1-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-yl]-1-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanol (**622**, 125.0 mg, 0.22 mmol) was dissolved in acetonitrile (11.7 mL) and trifluoroacetic acid (0.175 mL, 2.3 mmol) and triethylsilane (0.292 mL, 1.8 mmol) were added. The reaction was heated to reflux overnight. The reaction was concentrated, then washed with ethyl acetate and saturated sodium bicarbonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (0-60% ethyl acetate:hexanes) to provide the desired compound (**623**, 43 mg, 50%), consistent with the compound structure by ^{1}H-NMR.

Step 5 - Preparation of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (P-0388):

[0297] 5-[1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-vinyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (**623**, 0.043 g, 0.00011 mol) was dissolved in tetrahydrofuran (10 mL) and methanol (10 mL). The reaction was shaken under an atmosphere of hydrogen (30 psi) overnight. The reaction was filtered through Celite and the filtrate adsorbed onto silica and purified by silica gel column chromatography (ethyl acetate:hexanes) to provide the desired compound as a white solid (**P-0388**,

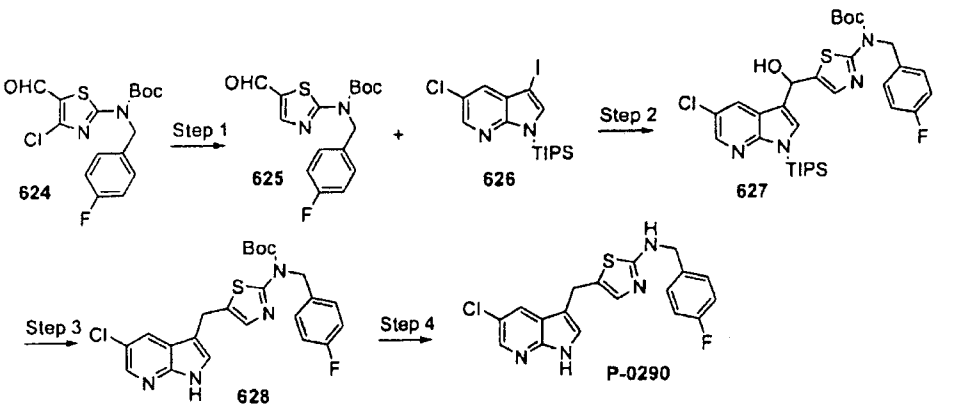
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2.1 mg, 5%), consistent with compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=397.6.

Example 42: Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine P-0290

[0298] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0290** was synthesized in four steps from (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester **624** as shown in Scheme 198.

Scheme 198



Step 1 - Preparation of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (625):

[0299] To a solution of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**624**, 1 g, 2.70 mmol, prepared as described in Example 5, Scheme 159, Step 2, where 4-(aminomethyl)pyridine **516** is replaced with p-fluorobenzylamine, i.e. intermediate in preparing compound **P-0156**) in methanol (100 mL) was added Pd/C (100 mg, 50% water wet) and sodium acetate (660 mg, 8.09 mmol) and the mixture was shaken under an atmosphere of hydrogen (50 psi) overnight observing ~50% conversion by LC/MS. The mixture was filtered over a bed of Celite and the solvent was removed *in vacuo* and purified by silica gel chromatography (ethyl acetate/heptane) to provide the desired compound as an off-white solid (450 mg, 50 %), consistent with compound structure by ^{1}H-NMR.

Step 2 - Preparation of {5-[(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-thiazol-2-yl}-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (627):

[0300] To a solution of 5-chloro-3-iodo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine (**626**, 300 mg, 0.69 mmol) in tetrahydrofuran (10 mL) at -20 °C was added dropwise iso-propyl-

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magnesium chloride (2M in tetrahydrofuran, 0.44 mL, 0.88 mmol). The reaction mixture was allowed to warm to 0 °C over 10 minutes and then cooled to -40 °C. To this reaction mixture was added a solution of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**625**, 211 mg, 0.63 mmol) in tetrahydrofuran (5 mL). The reaction mixture was allowed to warm to 0 °C over 30 minutes and then quenched with brine (50 mL). The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to give the crude material which was purified by silica gel column chromatography (0-30% ethyl acetate/heptane) to provide the desired compound as a foam (120 mg, 30%), consistent with structure by ^{1}H-NMR.

Step 3 - Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (628):

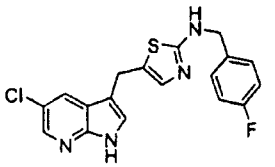
[0301] To a solution of {5-[(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-thiazol-2-yl}-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (**627**, 120 mg, 0.186 mmol) in acetonitrile (3 mL) was added trifluoroacetic acid (0.14 mL, 1.86 mmol) and triethylsilane (0.30 mL, 1.86 mmol). The resulting mixture was stirred for 2 hours at 40 °C. The solvent was then removed *in vacuo* and the residue was used directly in the next step.

Step 4: Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (P-0290):

[0302] To the solution of crude [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (**628**, 0.186 mmol theory) in dichloromethane (5 mL) at room temperature was added trifluoroacetic acid (1 mL) and the reaction was allowed to stir overnight. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate and then washed with saturated aqueous potassium carbonate making sure basicity was reached. The layers were separated and the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give the crude compound which was purified by silica gel chromatography (0-10% methanol/ethyl acetate). The solvent was removed *in vacuo* and the material was triturated with dichloromethane to give the desired compound as an off-white solid (20 mg, 29 % over 2 steps) consistent with compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=372.9.

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[0303] (4-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **P-0389**

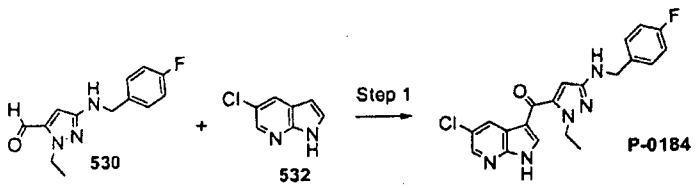


was synthesized following the protocol of Scheme 198, replacing 5-chloro-3-iodo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine **626** with 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96**, to provide the desired compound, consistent with structure by 1H-NMR and MS(ESI): $[M+H^+]^+$=339.0.

Example 43: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone P-0184

[0304] (5-Chloro-1H-pyrrolo[2,3-b]pyridin- 3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone **P-0184** was synthesized from 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** in 1 step as shown in Scheme 199.

Scheme 199



Step 1 - Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin- 3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone (P-0184):

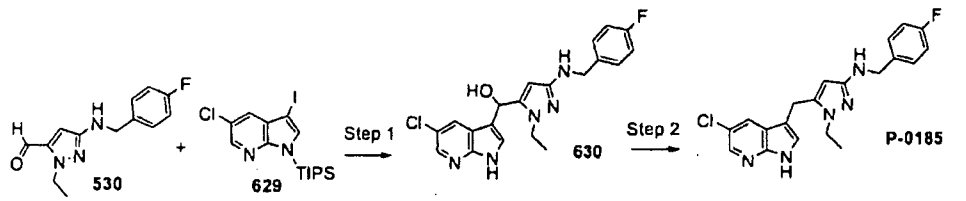
[0305] 5-Chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 0.068 g, 0.44 mmol) was combined with methanol (10 mL) and potassium hydroxide (0.16 g, 2.8 mmol). The mixture was stirred for 50 minutes, then 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 0.100 g, 0.40 mmol, prepared as described in Example 8, Scheme 162, Step 5) was added and the reaction was stirred overnight at room temperature and then concentrated. Ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate the solvent was removed under reduced pressure. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (10-100%) in hexanes provided the desired compound (0.0033 g, 2%). MS (ESI) $[M+H^+]^+$ = 398.1.

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Example 44: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine P-0185

[0306] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0185** was synthesized from 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **629** in 2 steps as shown in Scheme 200.

Scheme 200



Step 1 - Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanol (630):

[0307] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**629**, 0.15 g, 0.34 mmol) was dissolved in tetrahydrofuran (3 mL, 40 mmol) and the solution was cooled to -20 °C. 2 M isopropylmagnesium chloride in tetrahydrofuran (200 µL) was added dropwise and the reaction was stirred and allowed to warm to -5 °C. After the reaction was cooled to -20 °C, 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 0.043g, 0.17 mmol, prepared as described in Example 8, Scheme162, Step 5) in tetrahydrofuran (4 mL) was added to the mixture. The reaction was stirred and allowed to warm to -5 °C, then concentrated, ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (5-80%) in hexanes gave the desired compound (**630**, 0.038 g, 40%).

Step 2 - Synthesis of 5-(5-chloro-1H-pyrrolo[2,3-b]pyrid in-3-ylmethyl)-1-ethyl-1H-pyrazol-3 -yl]-(4-fluoro-benzyl)-amine (P-0185):

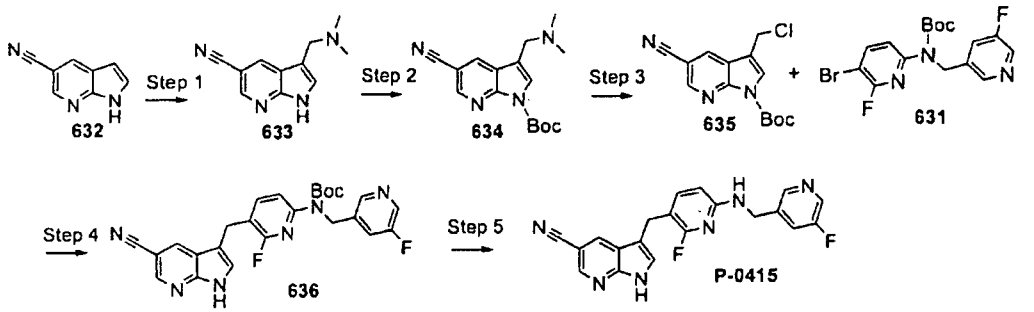
[0308] (5-Chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethy l-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanol (**630**, 0.045 g, 0.081 mmol) was dissolved in acetonitrile (5 mL) and triethylsilane (0.4 mL, 2.0 mmol) was added, followed by trifluoroacetic acid (0.2 mL, 2.0 mmol). The reaction was stirred at room temperature for 45 minutes, then stirred at 60 °C for 45 minutes. The solvent was removed under reduced pressure, ethyl acetate was added and the organic was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to dryness. Purification with silica gel

column chromatography eluting with a gradient of ethyl acetate (40-100%) in hexanes gave the desired compound (**P-0185**, 0.0068 g, 22%). MS (ESI) $[M+H^+]^+ = 384.1$.

Example 45: Synthesis of 3-2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile P-0415

[0309] 3-2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0415** was synthesized in 5 steps from 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile **632** as shown in Scheme 201.

Scheme 201



Step 1 – Synthesis of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (633):

[0310] To 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile (**632**, 3.00 g, 0.0210 mol) in isopropyl alcohol (120 mL) were added dimethylamine hydrochloride (1.91 g, 0.0235 mol) and formaldehyde (0.708 g, 0.0236 mol). The reaction was heated to reflux overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% to 30% methanol in dichloromethane containing 0.3% triethyl amine to give the desired compound (**633**, 2.0 g, 48%).

Step 2 – Synthesis of 5-cyano-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (634):

[0311] To 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**633**, 2.0 g, 0.010 mol) in tetrahydrofuran (60.0 mL) were added di-tert-butyldicarbonate (2.62 g, 0.0120 mol), 4-dimethylaminopyridine (0.12 g, 0.0010 mol) and triethylamine (4.0 mL, 0.029 mol). The reaction was stirred at 45 °C over a weekend, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 30% methanol in dichloromethane in hexane to give the

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desired compound (**634**, 2.50 g, 83%).

Step 3 – Synthesis of 3-chloromethyl-5-cyano-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (635):

[0312] To 5-cyano-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**634**, 2.60 g, 8.66 mmol) in toluene (60.0 mL) under an atmosphere of nitrogen was added ethyl chloroformate (0.828 mL, 8.66 mmol). 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 anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**635**, 400 mg, 16%).

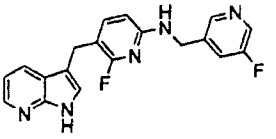
Step 4 – Synthesis of [5-(5-cyano-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (636):

[0313] To (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**631**, 0.600 g, 1.50 mmol, prepared as described in Example 21) in tetrahydrofuran (10.0 mL) at -25 °C under an atmosphere of nitrogen, was added a solution of isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.730 mL). The reaction was allowed to warm to 5 °C over 1 hour. The reaction was cooled to -35 °C, followed by addition of a solution of CuCN.2LiCl (0.65 M in tetrahydrofuran, 2.4 mL). After 5 minutes, 3-chloromethyl-5-cyano-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**635**, 0.086 g, 0.29 mmol) in tetrahydrofuran (4.0 mL) was added to the reaction. The reaction was allowed to warm to room temperature over 1 hour, then poured into a diluted ammonia solution, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**636**, 0.13 g, 92%). MS (ESI) $[M+H^+]^+ = 477.4$.

Step 5 – Synthesis of 3-2-fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0415):

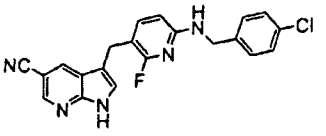
[0314] To [5-(5-cyano-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**636**, 0.130 g, 0.27 mmol) in dichloromethane (10.0 mL) was added trifluoroacetic acid (1.00 mL, 0.0130 mol). The reaction was stirred at room temperature overnight. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25% to 100% ethyl acetate in hexane to give a white solid (**P-0415**, 85.6 mg, 83.4%). MS (ESI) $[M+H^+]^+ = 377.0$.

[0315] (5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0414**



was prepared following the protocol of Scheme 201, substituting 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile **632** with 1H-Pyrrolo[2,3-b]pyridine in Step 1. MS (ESI) $[M+H^+]^+ = 352.5$.

[0316] 3-[6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0432**

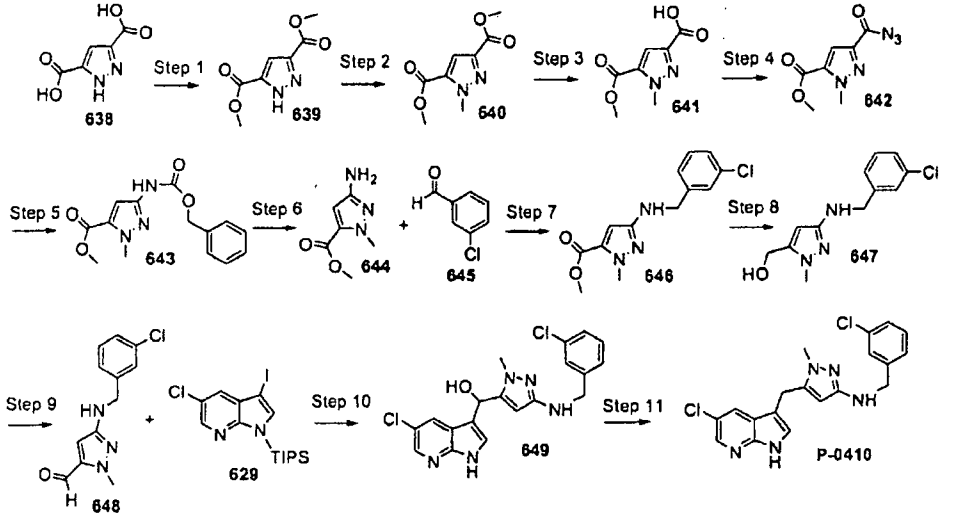


was prepared following the protocol of Scheme 201, replacing 5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **631** with (5-Bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester **637** (prepared as described in Example 21) in Step 4. MS (ESI) $[M+H^+]^+ = 391.9$.

Example 46: Synthesis of (3-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo [2,3-b] pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine P-0410

[0317] (3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo [2,3-b]pyridin-3-ylmethyl)-1- methyl-1H-pyrazol-3-yl]-amine **P-0410** was synthesized in 11 steps from 1H-pyrazole-3,5-dicarboxylic acid monohydrate **638** as shown in Scheme 202.

Scheme 202



Step 1 – Preparation of 1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (639):

[0318] 1H-Pyrazole-3,5-dicarboxylic acid monohydrate (**638**, 21.1 g, 121.0 mmol) was combined with methanol (350 mL) and hydrogen chloride (10 mL). The reaction was stirred at reflux overnight and then concentrated. The resulting solid was washed with ethyl acetate and hexanes and dried under reduced pressure. The obtained compound **639** was used without further purification. MS (ESI) $[M+H^+]^+ = 185.0$.

Step 2 – Preparation of 1-methyl-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (640):

[0319] 1H-Pyrazole-3,5-dicarboxylic acid dimethyl ester (**639**, 9.1 g, 49.0 mmol) was combined with acetone (400 mL) and potassium carbonate (10.2 g, 74.1 mmol). The mixture was stirred for 40 minutes under an atmosphere of nitrogen. To the stirring suspension, methyl iodide (3.4 mL, 54.0 mmol) was added dropwise. The reaction was stirred at room temperature overnight and then the solvent was evaporated under reduced pressure. The resulting solid was washed with water and filtered. After toluene was added, the solvent was removed under reduced pressure. The resulting compound **640** was used without further purification.

Step 3 – Preparation of 1-methyl-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (641):

[0320] 1-Methyl-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**640**, 3.7 g, 19.0 mmol) was combined with 1,4-dioxane (20 mL) and water (60 mL). Concentrated sulfuric acid (1.0 mL) in 2 mL of water was added to the solution. After the reaction was stirred at reflux overnight, it was cooled to room temperature and concentrated until precipitation began. The obtained mixture was left standing overnight. The resulting solid was filtered and dried under reduced pressure. The

collected aqueous fractions were extracted with ethyl acetate. The organic portion was dried over anhydrous sodium sulfate and concentrated. Additional solid was crystallized from ethyl acetate to give the desired compound (**641**, 2.33 g, 68%). MS (ESI) $[M+H^+]^+$ = 185.0, melting point 175 °C.

Step 4 – Preparation of 5-azidocarbonyl-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (642):

[0321] 1-Methyl-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (**641**, 3.2 g, 17.0 mmol) was combined with thionyl chloride (5 mL). The reaction was heated to reflux for 40 minutes and then concentrated twice from toluene. The resulting solid was dried under reduced pressure overnight. The product was dissolved into acetone (20 mL) and sodium azide (3.5 g, 54.0 mmol) was added in water (10 mL) rapidly at once. The obtained solution was stirred for one minute and then poured into ice-water (50mL). The precipitate was filtered and dried under reduced pressure. The final compound was used without further purification (**642**, 2.8 g, 77%).

Step 5 – Preparation of 5-benzyloxycarbonylamino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (643):

[0322] 5-Azidocarbonyl-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**642**, 2.8 g, 13.0 mmol) was combined with toluene (35 mL) and benzyl alcohol (2.1 mL, 20.0 mmol). The reaction was heated to reflux for 45 minutes and then the solvent was removed under reduced pressure. The compound (**643**, 2.4 g, 62%) was washed with methanol and dried under vacuum. MS (ESI) $[M+H^+]^+$ = 290.3.

Step 6 – Preparation of 5-amino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (644):

[0323] 5-Benzyloxycarbonylamino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**643**, 2.2 g, 7.6 mmol) was combined with methanol (50 mL) and 10% palladium on carbon (500 mg). The mixture was stirred under an atmosphere of hydrogen for three hours. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give the desired compound (**644**, 1.2 g, 98%). (ESI) $[M+H^+]^+$ = 156.1.

Step 7 – Preparation of 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (646):

[0324] 5-Amino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**644**, 1.3 g, 8.0 mmol) was combined with 3-chlorobenzaldehyde (**645**, 0.95 mL, 8.4 mmol) and acetonitrile (40 mL). Trifluoroacetic acid (3.2 mL, 42.0 mmol) was added followed by triethylsilane (6.7 mL, 42.0 mmol). The reaction was heated to reflux overnight and then concentrated. Ethyl acetate was added and the solution was washed with 1N potassium carbonate. The organic portion was dried over anhydrous sodium sulfate, filtered and concentrated. The compound (**646**, 0.944 g, 42%) was

crystallized from a mixture of ethyl acetate: hexane.

Step 8 – Preparation of [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-methanol (647):

[0325] 5-(3-Chloro-benzylamino)-2-methyl-2 H-pyrazole-3-carboxylic acid methyl ester (**646**, 0.944 g, 3.37 mmol) was combined with tetrahydrofuran (20 mL) and the solution was cooled to -40 °C. 1.0 M lithium tetrahydroaluminate in tetrahydrofuran (3.7 mL) was added and the reaction was stirred for 45 min at -20 °C. 1.0 M lithium tetrahydroaluminate in tetrahydrofuran (3.7 mL) was added at -40 °C and the reaction was stirred to 10°C. Sodium sulfate decahydrate was added in small portions and the mixture was stirred for two hours at room temperature, then filtered through Celite and concentrated. The resulting compound (**647**, 0.821 g, 97%) was washed with a mixture of ethyl acetate: hexanes and dried under reduced pressure.

Step 9 – Preparation of 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carbaldehyde (648):

[0326] [5-(3-Chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-methanol (**647**, 0.821 g, 3.26 mmol) was combined with dichloromethane (70 mL) and manganese(IV) oxide (4 g). The reaction was stirred at room temperature overnight under an atmosphere of nitrogen. The mixture was filtered through Celite and concentrated. Purification by silica gel column chromatography eluting with a gradient of ethyl acetate (10-100%) in hexane gave the desired aldehyde (**648**, 0.482 g, 60%).

Step 10 – Preparation of [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (649):

[0327] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**629**, 0.19 g, 0.44 mmol) was dissolved in tetrahydrofuran (0.9 mL). The solution was cooled to -20 °C. 2M isopropylmagnesium chloride in tetrahydrofuran (200 μL) was added dropwise to the mixture, then stirred to -5 °C. After the reaction was cooled to -20 °C, 5-(3-chloro-benzylamino)-2-methyl-2 H-pyrazole-3-carbaldehyde (**648**, 0.050 g, 0.20 mmol) in 2 mL of tetrahydrofuran was added at once to the mixture. The reaction was stirred to 0 °C and then concentrated. Ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. The organic portion was dried over anhydrous sodium sulfate and concentrated. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (5-80%) in hexane gave the desired compound (**649**, 0.033 g, 30%). (ESI) $[M+H^+]^+ = 558.3, 560.9$.

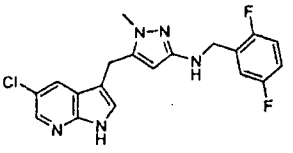
Step 11 – Preparation of (3-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine (P-0410):

[0328] [5-(3-Chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**649**, 0.033 g, 0.059 mmol) was combined with

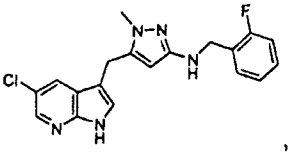
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dichloromethane (5 mL, 0.08 mol) and triethylsilane (200 μL, 1.0 mmol) was added, followed by trifluoroacetic acid (100 μL, 1.0 mmol). The reaction was stirred at room temperature overnight and then concentrated. Ethyl acetate was added and the organic portion was washed with 1 M potassium carbonate, dried over anhydrous sodium sulfate and concentrated. Purification with silica gel flash chromatography eluting with a gradient of methanol (2-20%) and dichloromethane followed by washes with a mixture of ethyl acetate:hexane gave the desired compound (**P-0410**, 0.0039 g, 17%). (ESI) $[M+H^+]^+ = 387.30$.

[0329] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2,5-difluoro-benzyl)-amine **P-0411** and [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2-fluoro-benzyl)-amine **P-0413**,



and



, respectively,

were prepared following the protocol of Scheme 202, replacing 3-chlorobenzaldehyde **645** with 2,5-difluorobenzaldehyde and 2-fluorobenzaldehyde, respectively, in Step 7. (ESI) $[M+H^+]^+ = 389.95$ (**P-0411**) and 370.20 (**P-0413**).

Example 47: Enzyme activity assays

[0330] Assays for the activity of c-Kit or c-Fms are known in the art, for example as described in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety. Similar assays may be used to assess the activity of TrkA, TrkB, and HGK.

[0331] Additional cell based assays can be correlated to the Fms activity of compounds of the invention. For example, the ability of osteoclast precursor cells (commercially available from Lonza) to differentiate into mature osteoclasts, due to stimulation by M-CSF and RANKL, in the presence of compounds, can be measured using a method analogous to that previously reported (Hudson et al., Journal of Urology, 1947, 58:89-92), where the amount of acid phosphatase in the supernatant (i.e. TRAP5b excreted by mature osteoclasts) is proportional to the number of mature osteoclasts present. In another example, the ability of M-CSF-dependent murine macrophage cells (BAC1.2F5) to proliferate in the presence of compounds can be measured by culturing cells as previously described (Morgan et al., Journal of Cellular Physiology, 1987, 130:420-427) and

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determining cell viability by analysis of ATP levels in the cell culture (Crouch et al., Journal of Immunological Methods, 1993, 160:81-8).

[0332] Compounds P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0107, P-0108, P-0109, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0118, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0131, P-0132, P-0138, P-0143, P-0144, P-0145, P-0148, P-0154, P-0156, P-0157, P-0159, P-0161, P-0163, P-0170, P-0171, P-0173, P-0174, P-0176, P-0177, P-0179, P-0180, P-0181, P-0182, P-0186, P-0187, P-0188, P-0190, P-0192, P-0193, P-0194, P-0195, P-0197, P-0199, P-0201, P-0203, P-0205, P-0206, P-0208, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0221, P-0222, P-0224, P-0225, P-0226, P-0228, P-0234, P-0237, P-0239, P-0240, P-0242, P-0243, P-0244, P-0245, P-0246, P-0252, P-0253, P-0255, P-0257, P-0258, P-0259, P-0260, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0294, P-0297, P-0298, P-0301, P-0302, P-0303, P-0305, P-0306, P-0307, P-0308, P-0309, P-0311, P-0312, P-0313, P-0314, P-0316, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0334, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0350, P-0351, P-0352, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0361, P-0362, P-0363, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0375, P-0376, P-0377, P-0378, P-0379, P-0382, P-0383, P-0385, P-0387, P-0390, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0404, P-0406, P-0407, P-0408, P-0409, and P-0412 demonstrated an IC_{50} of less than 1 μM in at least one of the c-kit assays described in US Patent Application Publication number US 2007/0032519.

[0333] Compounds P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0106, P-0107, P-0108, P-0109, P-0110, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0117, P-0118, P-0119, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0130, P-0131, P-0132, P-0134, P-0135, P-0136, P-0137, P-0140, P-0141, P-0142, P-0143, P-0144, P-0145, P-0146, P-0147, P-0148, P-0149, P-0150, P-0151, P-0152, P-0153, P-0154, P-0156, P-0157, P-0158, P-0159, P-0160, P-0161, P-0163, P-0164, P-0165, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0175, P-0176, P-0179, P-0180, P-0181, P-0182, P-0183, P-0185, P-0186, P-0187, P-0188, P-0189, P-0190, P-0191, P-0192, P-0193, P-0194, P-0195, P-0196, P-0197, P-0198, P-0199, P-0200, P-0201, P-0202, P-0203, P-0204, P-0205, P-0206, P-0207,

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P-0208, P-0209, P-0210, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0232, P-0233, P-0234, P-0235, P-0236, P-0237, P-0238, P-0239, P-0240, P-0241, P-0242, P-0243, P-0244, P-0245, P-0246, P-0247, P-0248, P-0249, P-0250, P-0251, P-0252, P-0253, P-0254, P-0255, P-0256, P-0257, P-0258, P-0259, P-0260, P-0261, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0292, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0299, P-0300, P-0301, P-0302, P-0303, P-0304, P-0305, P-0306, P-0307, P-0308, P-0309, P-0310, P-0311, P-0312, P-0313, P-0314, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0333, P-0334, P-0335, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0349, P-0350, P-0351, P-0352, P-0353, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0360, P-0361, P-0362, P-0363, P-0364, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0374, P-0375, P-0376, P-0377, P-0378, P-0379, P-0380, P-0381, P-0382, P-0383, P-0384, P-0385, P-0386, P-0387, P-0390, P-0391, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0403, P-0404, P-0405, P-0406, P-0407, P-0408, P-0409, and P-0412 had IC_{50} of less than 1 μM in at least one of the Fms assays described in US Patent Application Publication number US 2007/0032519.

[0334] Compounds were similarly assayed to determine IC_{50} values with respect to inhibition of TrkA kinase activity, for which compounds P-0157, P-0171, P-0179, P-0180, P-0303 and P-0412 had IC_{50} of less than 1 μM. in this TrkA assay. Compounds were similarly assayed to determine IC_{50} values with respect to inhibition of HGK kinase activity, for which compounds P-0156, P-0177, P-0179, P-0195, P-0201, P-0203, P-0206, P-0207, P-0231, P-0240, P-0241, P-0255, P-0324, P-0341, and P-0403 had IC_{50} of less than 1 μM.

[0335] 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.

[0336] 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

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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.

[0337] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, variations can be made to provide additional compounds of Formulae II or III and/or various methods of administration can be used. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0338] 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. 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.

[0339] 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.

[0340] 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.

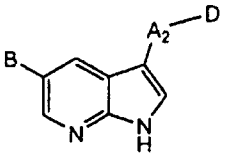
[0341] Thus, additional embodiments are within the scope of the invention and within the following claims.

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CLAIMS

What is claimed is:

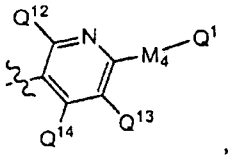
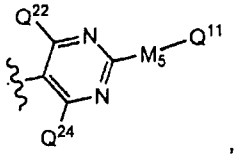
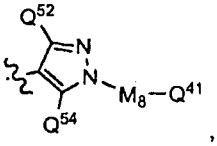
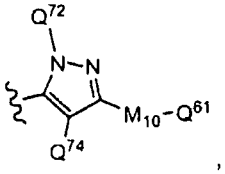
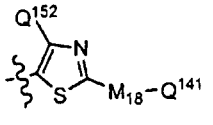
1. A compound having the chemical structure of Formula II,



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

D has a structure selected from the group consisting of





, and


in which  indicates the attachment point of D to A_2 of Formula II;

A_2 is $-CH_2-$ or -C(O)-;

B is selected from the group consisting of hydrogen, -CN, $-OR^{41}$, $-SR^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as B, or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

M_4 is $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, or $-NR^{39}C(O)-$;

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M_5, M_{10}, and M_{18} are selected from the group consisting of a bond, $-NR^{39}-$, -S-, -O-, $-NR^{39}CH_2-$, $-NR^{39}CH_2CH_2-$, $-NR^{39}CH(R^{40})-$, $-SCH_2-$, $-OCH_2-$, $-C(O)NR^{39}-$, $-S(O)_2NR^{39}-$, $-CH_2NR^{39}-$, $-CH(R^{40})NR^{39}-$, $-NR^{39}C(O)-$, and $-NR^{39}S(O)_2-$;

M_8 is selected from the group consisting of a bond, $-CH_2-$, $-CH_2C(O)-$, $-S(O)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2CH_2CH_2-$, $-S(O)_2NR^{39}-$, $-S(O)_2NR^{39}CH_2-$, $-S(O)_2NR^{39}CH(CH_3)-$, $-S(O)_2NR^{39}CH_2CH_2-$, $-C(O)-$, $-C(O)CH_2-$, $-C(O)CH(CH_3)-$, $-C(O)CH_2CH_2-$, $-C(O)NR^{39}-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, and $-C(O)NR^{39}CH_2CH_2-$;

Q^1 is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as Q^1 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{11}, Q^{41}, Q^{61}, and Q^{141} are lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein lower alkyl is optionally substituted with one or more fluoro, lower alkoxy, or fluoro substituted lower alkoxy, and wherein cyclaolkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of Q^{11}, Q^{41}, Q^{61}, or Q^{141}, or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{12} is fluoro, chloro or $-CF_3$;

Q^{13} and Q^{14} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl;

Q^{22}, Q^{24}, Q^{52}, and Q^{54} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, $-NR^{44}R^{44}$, $-OR^{44}$, and $-SR^{44}$, provided, however, that at least one of Q^{22} and Q^{24} and at least one of Q^{52} and Q^{54} is hydrogen, fluoro, chloro, lower alkyl or fluoro substituted lower alkyl;

Q^{74} and Q^{152} are hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, $-NR^{44}R^{44}$, $-OR^{44}$, or $-SR^{44}$;

Q^{72} is hydrogen, lower alkyl or fluoro substituted lower alkyl;

R^{39} at each occurrence is independently hydrogen or lower alkyl;

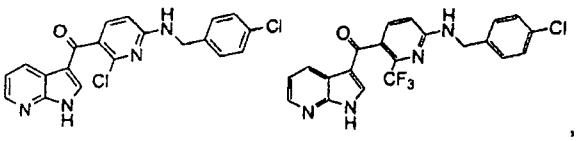
R^{40} is lower alkyl or fluoro substituted lower alkyl;

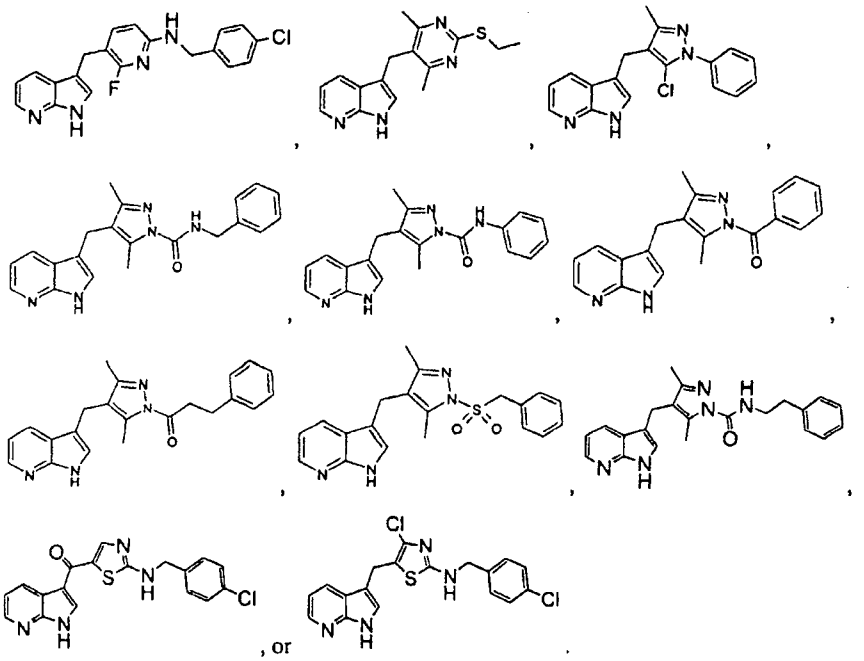
R^{41} at each occurrence is independently selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{41} or as substituents of lower alkyl are are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^{42} at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy; and

each R^{44} is independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

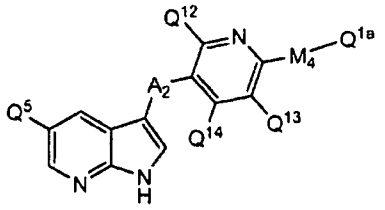
provided, however, that the compound is not





, or

2. The compound of Claim 1 having the structure of Formula IIa,



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

Q^{1a} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$;

Q^5 is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

A_2, M_4, Q^{12}, Q^{13}, Q^{14} and R^{41} are as defined for Claim 1.

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3. The compound of Claim 2 selected from the group consisting of:

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

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

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

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

{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,

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

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

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

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

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

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

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

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

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

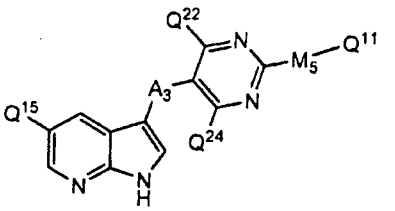
3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,

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

all salts, prodrugs, tautomers, and isomers thereof.

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4. A compound of Claim 1 having the structure of Formula IIb



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_3 is $-CH_2-$ or -C(O)-;

Q^{15} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_5, Q^{11}, Q^{22}, Q^{24}, and R^{41}, are as defined for Formula II.

5. The compound of Claim 4 selected from the group consisting of:
(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,6-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-benzyl)-amine,
(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

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amine,
(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine,
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine,
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine, (3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(5-Chloro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-trifluoromethyl-benzyl)-amine,
(3-Chloro-2-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-3-trifluoromethyl-

benzyl)-amine,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-4-trifluoromethyl-benzyl)-amine,

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

(2-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,

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

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

(2-Chloro-5-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,

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

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-pyrrolidin-1-yl-ethyl)-amine,

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine,

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

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

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

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

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

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

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

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

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

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

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

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

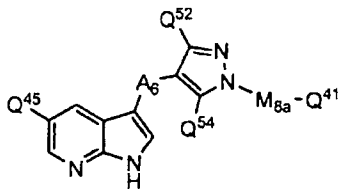
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-benzyl)-amine,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-ethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexylmethyl-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine,
[2-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-difluoromethoxy-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methoxy-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-ethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-benzyl)-amine,
(3-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-ethoxy-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-morpholin-4-yl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-difluoromethoxy-benzyl)-amine,
(4-Chloro-3-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(3-fluoro-phenyl)-ethyl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-dimethylamino-benzyl)-amine; and
all salts, prodrugs, tautomers, and isomers thereof.

6. The compound of Claim 4 selected from the group consisting of:
(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-benzyl)-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine; and all salts, prodrugs, tautomers, and isomers thereof.

7. The compound of Claim 1 having the chemical structure of Formula IIe,



all salts, prodrugs, tautomers, and isomers thereof,
wherein:

A_6 is $-CH_2-$ or -C(O)-;

M_{8a} is selected from the group consisting of $-CH_2-$, $-CH_2C(O)-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(R^{40})-$, and $-C(O)NR^{39}CH_2CH_2-$;

Q^{45} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

Q^{41}, Q^{52}, Q^{54}, R^{39}, R^{40}, and R^{41} are as defined for Claim 1.

8. The compound of Claim 7 selected from the group consisting of:
3-(1-Benzyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine,
2-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-1-phenyl-ethanone,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-chloro-benzylamide,
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-fluoro-benzylamide,
3-[3,5-Dimethyl-1-(5-trifluoromethyl-furan-2-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-

b]pyridine,

3-[3,5-Dimethyl-1-(5-methyl-isoxazol-3-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-chloro-benzylamide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-methoxy-benzylamide,

3-{3,5-Dimethyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-pyrazol-4-ylmethyl}-1H-pyrrolo[2,3-b]pyridine,

3-[3,5-Dimethyl-1-(4-methyl-2-phenyl-thiazol-5-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methoxy-benzylamide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid ((S)-1-phenyl-ethyl)-amide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-fluoro-benzylamide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-fluoro-benzylamide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methyl-benzylamide,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methyl-benzylamide,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-fluoro-benzylamide,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-

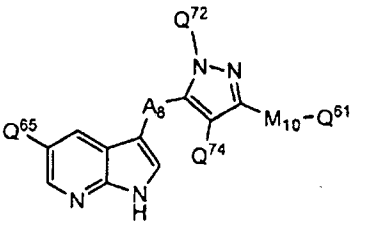
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chloro-benzylamide,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [(S)-1-(4-fluoro-phenyl)-ethyl]-amide; and

all salts, prodrugs, tautomers, or isomers thereof.

9. A compound of Claim **1** having the chemical structure of Formula IIg,



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_8 is $-CH_2-$, or $-C(O)-$;

Q^{65} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_{10}, Q^{61}, Q^{72}, Q^{74}, and R^{41} are as defined for Claim 1.

10. The compound of Claim **9** selected from the group consisting of:

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

(4-Fluoro-benzyl)-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-amine,

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

(4-Fluoro-benzyl)-{1-methyl-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-1H-pyrazol-3-yl}-amine,

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone,

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

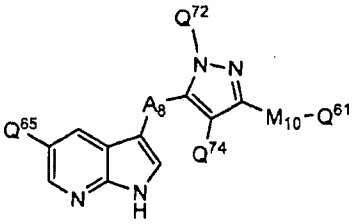
3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,

(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-

amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2,5-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2-fluoro-benzyl)-amine; and
all salts, prodrugs, tautomers, or isomers thereof.

11. The compound of Claim 9 is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine, 3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile, or any salts, prodrugs, tautomers, or isomers thereof.

12. A compound of Claim 1 having the chemical structure of Formula IIp,



all salts, prodrugs, tautomers, and isomers thereof,
wherein:

A_8 is $-CH_2-$, or -C(O)-;

Q^{65} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_{10}, Q^{61}, Q^{72}, Q^{74}, and R^{41} are as defined for Claim 1.

13. The compound of Claim 12 selected from the group consisting of:
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine,
[4-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine,
(4-Fluoro-benzyl)-[4-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-2-ylmethyl-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-

amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amine,
[2-(4-Fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone,
{2-[(4-Chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-thiazol-2-ylmethyl-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine,
Benzyl-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine,
(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-2H-pyrazol-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-thiazol-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-methyl-thiazol-5-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-chloro-pyridin-2-ylmethyl)-amine,

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

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ylmethyl)-amine,
(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3,5-dichloro-pyridin-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-trifluoromethyl-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine; and
all salts, prodrugs, tautomers, or isomers thereof.

14. The compound of Claim 12 selected from the group consisting of:
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine,
(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine,

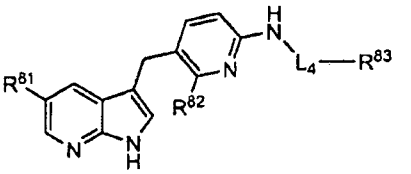
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-thiazol-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-chloro-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-chloro-pyridin-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1-ethyl-1H-pyrazol-4-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-phenethyl-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-difluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-fluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine,
(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine,
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-

pyridin-2-ylmethyl)-amine,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine; and

all salts, prodrugs, tautomers, or isomers thereof.

15. A compound having the chemical structure of Formula III,



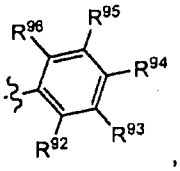
all salts, prodrugs, tautomers, and isomers thereof,

wherein:

L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, -C(O)- or -C(O)NH-;

R^{81} is selected from the group consisting of hydrogen, $-OR^{41}$, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

R^{82} is selected from the group consisting of hydrogen, C_{1-3} alkyl, fluoro substituted C_{2-3} alkyl, OH, C_{1-3} alkoxy, and fluoro substituted C_{1-3} alkoxy;

R^{83} is heterocycloalkyl, heteroaryl, or  , in which  indicates the attachment point of R^{83} to L_4 of Formula III, wherein heterocycloalkyl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

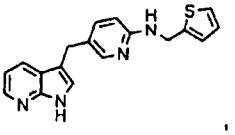
R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

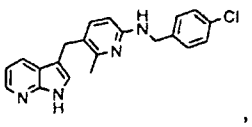
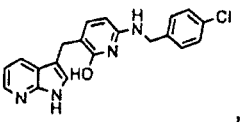
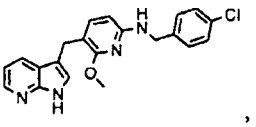
R^{40} is selected from the group consisting of lower alkyl, and fluoro substituted lower alkyl;

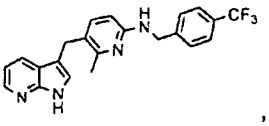
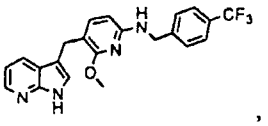
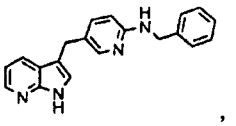
R^{41} at each occurrence is independently selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro,

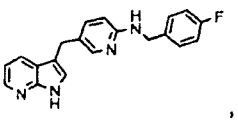
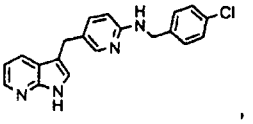
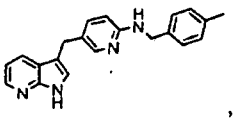
lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{41} or as substituents of lower alkyl are are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

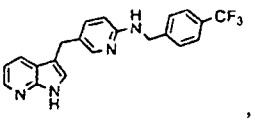
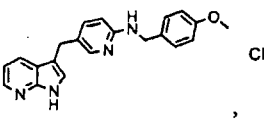
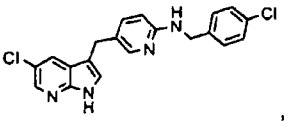
R^{42} at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy;

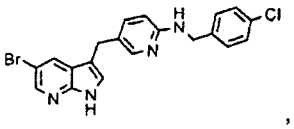
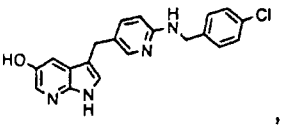
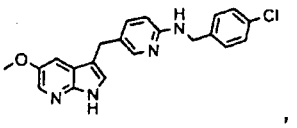
provided, however, that the compound is not  ,

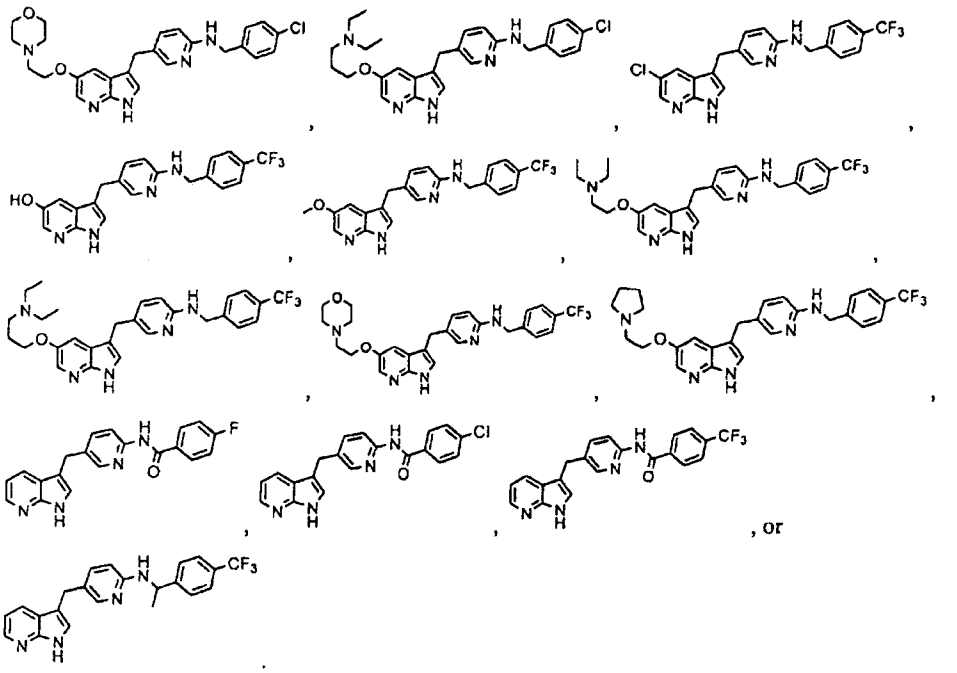
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16. The compound of Claim **15** selected from the group consisting of:

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

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

2-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide,

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide,

5-Methyl-pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide,

3-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide,

4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide,

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide,

3-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide,

3,4-Difluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide,

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

((R)-1-Phenyl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,

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

[1-(2-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,

[2-(3-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,

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(3-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
(3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
Phenethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(5-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(3-Fluoro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(6-Methoxy-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
(3,5-Dichloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(6-Morpholin-4-yl-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
3-{6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine,
3-[6-(2-Fluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
(2-Fluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
3-[6-(2-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-

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carbonitrile,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
3-[6-(2,6-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine,
(2-Chloro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
3-[6-(2-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine,
3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine,
3-[6-(2-Trifluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
3-[6-(2-Ethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile; and all salts, prodrugs, tautomers, or isomers thereof.

17. A composition comprising a pharmaceutically acceptable carrier and a compound according to any of Claims **1-16**.

18. A method for treating a subject suffering from or at risk of a c-kit and/or c-fms mediated disease or condition, comprising administering to the subject an effective amount of a compound of any of Claims **1-16**.

19. The method of Claim **18**, wherein the disease or condition is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or

other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome, multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, osteomyelitis, peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

20. The method of Claims **19**, wherein the compound is approved for administration to a human.

21. A kit comprising a composition according to Claim **17**.

22. The kit of Claim **21**, wherein the composition is approved for a medical indication selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome, multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, osteomyelitis, peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

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COMPUESTOS QUE MODULAN ACTIVIDAD C-FMS Y/O C-KIT Y USOS PARA ELLO

SOLICITUDES DE PATENTE RELACIONADAS

[0001] Esta solicitud reclama prioridad a la Solicitud Provisional Estadounidense No. 60/860,749, titulada "Compuestos que Modulan la Actividad c-Fms y c-Kit y Usos Para ello", presentada el 22 de noviembre de 2006, y se relaciona con la Solicitud de Patente Norteamericana No. 11/435,381, titulada "Compuestos que Modulan la Actividad c-Kit y c-Fms y Usos Para ello", presentada el 16 de mayo de 2006, que reclama el beneficio de la Solicitud Provisional Estadounidense No. 60/682,063, titulada "Compuestos que Modulan la Actividad c-Kit y Usos Para ello", presentada el 17 de mayo de 2005, Solicitud Provisional Estadounidense No. 60/682,051, titulada "Compuestos que Modulan la Actividad c-Fms y Usos Para ello", presentada el 17 de mayo de 2005, Solicitud Provisional Estadounidense No. 60/682,042, titulada "Compuestos que Modulan la Actividad c-Kit y c-Fms y Usos Para ello", presentada el 17 de mayo de 2005, Solicitud Provisional Estadounidense No. 60/692,750, titulada "Compuestos que Modulan la Actividad c-Kit y c-Fms y Usos Para ello", presentada el 22 de junio de 2005, y Solicitud Provisional Estadounidense No. 60/692,960, titulada "Compuestos y Métodos para Modulación de Cinasas, e Indicaciones Para ello", presentada el 22 de junio de 2005, todas las cuales se incorporan en este documento como referencia en sus totalidades y para todos las propósitos.

CAMPO DE LA INVENCIÓN

[0002] Esta invención se relaciona con ligandos para c-fms y c-kit, y con métodos para el uso de los mismos. La información proporcionada pretende solamente ayudar a la comprensión del lector. Nada de la información proporcionada ni las referencias citadas se admite como técnica anterior a la presente invención. Cada una de las referencias citadas se incorpora en este documento en su totalidad y para cualquier propósito.

ANTECEDENTES DE LA INVENCIÓN

[0003] C-fms y c-kit son tipo III proteína tirosina cinasas receptoras transmembranales (RPTKs)

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que regulan cascadas clave de transducción de señales que controlan crecimiento y proliferación celular. Ambos receptores tienen atributos estructurales similares que comprenden cinco dominios extracelulares de inmunoglobulina (IG), un único dominio transmembranal, y un dominio de cinasa citoplásmico dividido, separado por un segmento de inserto de cinasa.

c-Fms

[0004] C-fms es un miembro de la familia de genes originalmente aislados de la cepa Susan McDonough de virus de sarcoma felino. El proto-oncogen celular FMS (c-fms, sarcoma felino celular de McDonough) codifica el receptor para el factor estimulante de colonias de macrófagos (M-CSF). C-fms es crucial para el crecimiento y diferenciación del linaje monocito-macrófago, y con la unión de M-CSF al dominio extracelular de c-fms, el receptor se dimeriza y trans-autofosforila residuos citoplásmicos de tirosina.

[0005] 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 de citocinas secundarias 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 diferenciación de trofoblastos (Motoyoshi, Int J Hematol. 1998, 67:109-22). Los elevados niveles séricos de M-CSF en el embarazo temprano pueden participar en los mecanismos inmunológicos responsables del mantenimiento del embarazo (Flanagan & Lader, Curr Opin Hematol. 1998, 5:181-5).

[0006] Se relacionan con c-fms y c-kit dos receptores del factor de crecimiento derivado de plaquetas, alfa (es decir, pdgfra) y beta (pdgfrb) (PDGF). El gen que codifica pdgfra se ubica en el cromosoma 4q11-q12 en la misma región del cromosoma 4 que el oncogen que codifica c-kit. Los

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genes que codifican pdgfra y c-fms parecen haber evolucionado de un gen ancestral común por duplicación génica, considerando que estos dos genes se enlazan en tándem en el cromosoma 5. Se orientan cabeza a cola con el exón 5 prima del gen c-fms ubicado sólo 500 bp desde el último 3 prima exón del gen que codifica pdgfra. La mayor parte de los tumores de estroma gastrointestinal (GIST) tienen mutaciones de activación en c-kit, y la mayor parte de los pacientes con GISTs responden bien a Gleevec, que inhibe c-kit. Heinrich et al. (Science 2003, 299:708-10) han mostrado que aproximadamente 35% de los GISTs que carecen de mutaciones de c-kit tienen mutaciones de activación intragénica en el gen que codifica pdgfra, y que los tumores que expresan c-kit o pdgfra son indistinguibles con respecto a la activación de intermediarios de señalización corriente abajo y cambios citogenéticos asociados con progresión tumoral. De esta manera, las mutaciones en c-kit y pdgfra parecen ser mecanismos oncogénicos alternativos y mutuamente exclusivos en GISTs.

[0007] 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 resalta un papel para c-fms en las enfermedades, tales como, por ejemplo, enfermedades inflamatorias. Más particularmente, dado que elevados niveles de M-CSF se encuentran en el estado de enfermedad, la modulación de la actividad de c-fms puede aminorar la enfermedad asociada con niveles incrementados de M-CSF.

c-Kit

[0008] El receptor del Factor de Células Madre (SCF) c-kit juega un importante papel en el desarrollo de melanocitos y mastocitos, células germinales y hematopoyéticas. El Factor de Células Madre (SCF) es un 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 fisiológico para c-kit.

[0009] SCF se sintetiza como una proteína transmembranal con un peso molecular de 220 o 248

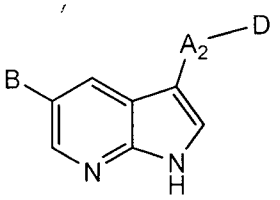
Daltones, dependiendo de la edición alternativa del mRNA para codificar el exón 6. La proteína mayor puede escindirse proteolíticamente para formar una proteína glicosilada soluble, que se dimeriza de manera no covalente. Las formas soluble y unida a membrana de SCF pueden unirse y activar a c-kit. Por ejemplo, en la piel, SCF se expresa predominantemente por fibroblastos, queratinocitos, y células endoteliales, que modulan la actividad de melanocitos y mastocitos que expresan c-kit. En médula ósea las células de estroma expresan SCF y regulan la hematopoyesis de células madre que expresan c-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 c-kit en las células germinales.

SUMARIO DE LA INVENCIÓN

[0010] La presente invención se relaciona con compuestos activos sobre c-fms, c-kit, o tanto c-fms como c-kit. De conformidad con un aspecto de la presente invención, se ha descubierto que en el tratamiento de enfermedades sensibles al tratamiento por una cantidad efectiva de un modulador de c-fms solo o c-kit solo, la eficacia del tratamiento puede aumentarse si dichos compuestos son inhibidores duales tanto de c-fms como de c-kit. En otro aspecto de la presente invención, los compuestos activos sobre c-fms, c-kit, o tanto c-fms como c-kit también son activos sobre una o más de TrkA, TrkB y HGK. En particular, la invención proporciona compuestos de la Fórmula II, y todas las fórmulas sub-genéricas de los mismos (por ejemplo, Fórmula IIa, IIb, IIe, IIg y IIp), Fórmula III, o compuestos adicionales como se describe en los ejemplos sintéticos, así como métodos para usar tales compuestos como se describe a continuación. De esta manera, la invención proporciona métodos para usar compuestos que pueden usarse de manera terapéutica y/o profiláctica, que implican modulación de c-fms, c-kit, o tanto c-fms como c-kit, o que implican una o más de TrkA, TrkB y HGK además de c-fms, c-kit, o tanto c-fms como c-kit.

[0011] Los compuestos de la Fórmula II tienen la siguiente estructura:

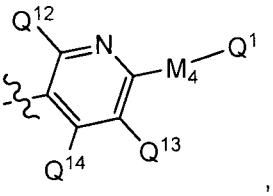
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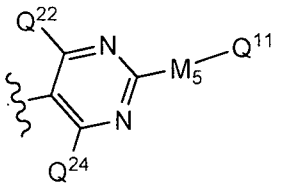
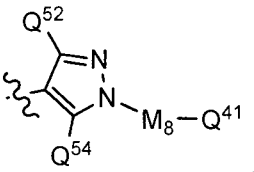
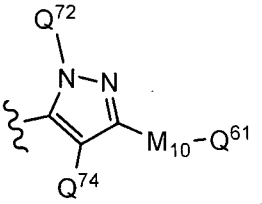


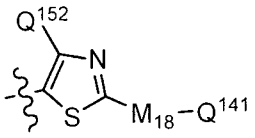
Fórmula II

todas las sales, profármacos, tautómeros, e isómeros de los mismos,

en donde:

D tiene una estructura seleccionada del grupo que consiste de  ,

 ,  ,  y



en que  indica el punto de unión de D a A_2 de la Fórmula II;

A_2 es $-CH_2-$ o -C(O)-;

B se selecciona del grupo que consiste de hidrógeno, -CN, $-OR^{41}$, $-SR^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, $-C(O)NR^{39}R^{41}$, $-C(O)R^{41}$, $-S(O)_2NR^{39}R^{41}$, $-S(O)_2R^{41}$, halógeno, alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo como B, o como sustituyentes de alquilo inferior, se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, -

NO_2, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

M_4 es $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, o $-NR^{39}C(O)-$;

M_5, M_{10}, y M_{18} se seleccionan del grupo que consiste de un enlace, $-NR^{39}-$, -S-, -O-, $-NR^{39}CH_2-$, $-NR^{39}CH_2CH_2-$, $-NR^{39}CH(R^{40})-$, $-SCH_2-$, $-OCH_2-$, $-C(O)NR^{39}-$, $-S(O)_2NR^{39}-$, $-CH_2NR^{39}-$, $-CH(R^{40})NR^{39}-$, $-NR^{39}C(O)-$, y $-NR^{39}S(O)_2-$;

M_8 se selecciona del grupo que consiste de un enlace, $-CH_2-$, $-CH_2C(O)-$, $-S(O)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2CH_2CH_2-$, $-S(O)_2NR^{39}-$, $-S(O)_2NR^{39}CH_2-$, $-S(O)_2NR^{39}CH(CH_3)-$, $-S(O)_2NR^{39}CH_2CH_2-$, -C(O)-, $-C(O)CH_2-$, $-C(O)CH(CH_3)-$, $-C(O)CH_2CH_2-$, $-C(O)NR^{39}-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, y $-C(O)NR^{39}CH_2CH_2-$;

Q^1, Q^{11}, Q^{41}, Q^{61}, y Q^{141} son arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halógeno, alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo como sustituyentes de Q^1, Q^{11}, Q^{41}, Q^{61}, o Q^{141}, o como sustituyentes de alquilo inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

Q^{12} es flúor, cloro o $-CF_3$;

Q^{13} y Q^{14} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor;

Q^{22}, Q^{24}, Q^{52}, y Q^{54} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NR^{44}R^{44}$, $-OR^{44}$, y $-SR^{44}$,

siempre y cuando, sin embargo, al menos uno de Q^{22} y Q^{24} y al menos uno de Q^{52} y Q^{54} sea hidrógeno, flúor, cloro, alquilo inferior o alquilo inferior sustituido con flúor;

Q^{74} y Q^{152} son hidrógeno, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, -$NR^{44}R^{44}$, -OR^{44}, o –SR^{44}; Q^{72} es hidrógeno, alquilo inferior o alquilo inferior sustituido con flúor;

R^{39} en cada caso se selecciona independientemente del grupo que consiste de hidrógeno y alquilo inferior;

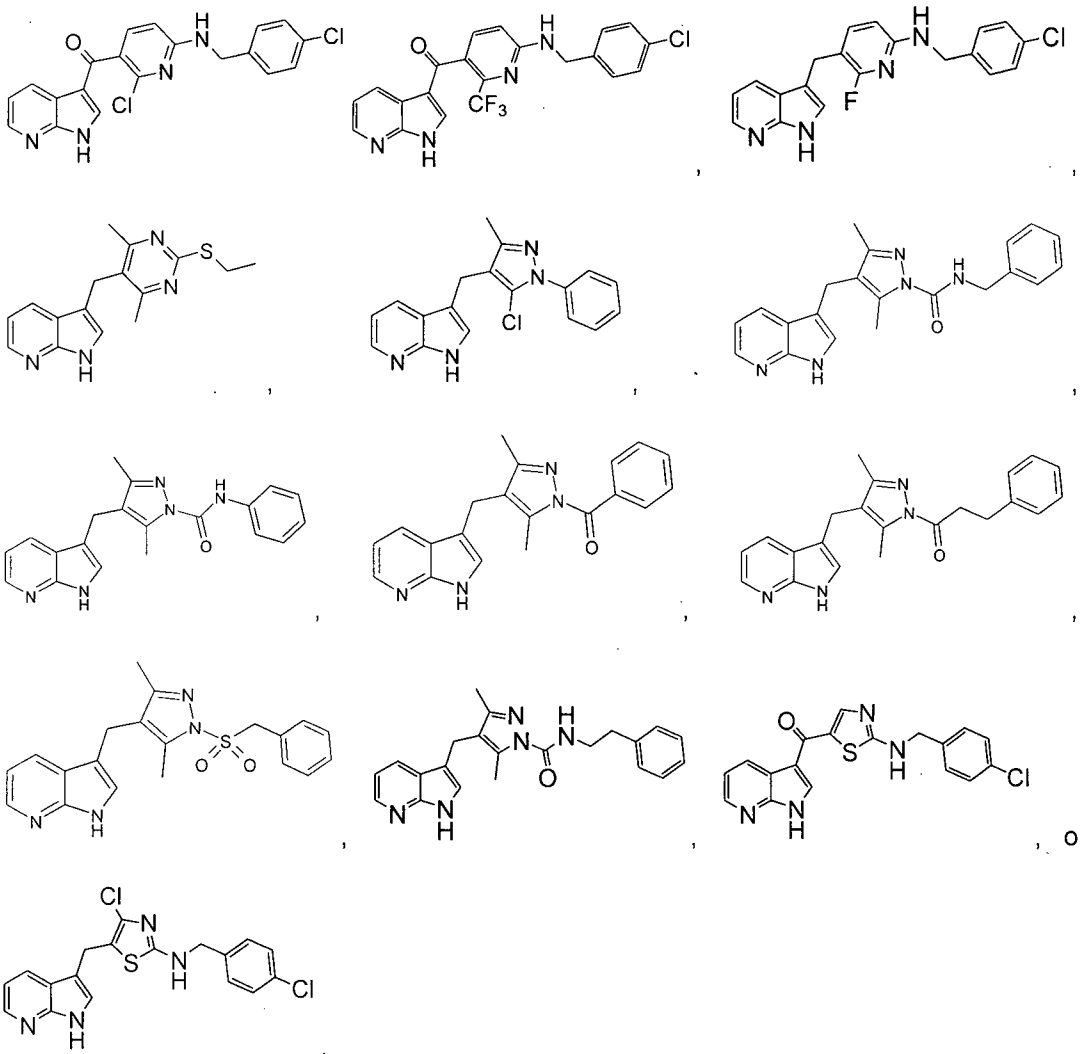
R^{40} se selecciona del grupo que consiste de alquilo inferior, y alquilo inferior sustituido con flúor;

R^{41} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, como R^{41} o como sustituyentes de alquilo inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^{42}, -SR^{42}, -NHR^{42}, -$NR^{42}R^{42}$, -$NR^{39}C(O)R^{42}$, -$NR^{39}S(O)_2R^{42}$, -$S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

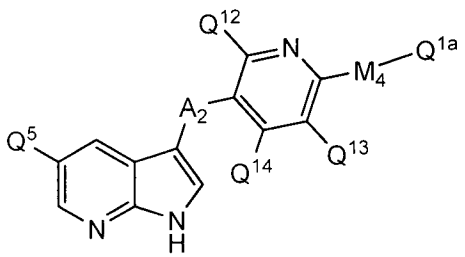
R^{42} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, heterocicloalquilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, y cicloalquilamino, y en donde el heterocicloalquilo y heteroarilo se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior y alcoxi inferior sustituido con flúor; y

cada R^{44} es independientemente hidrógeno, alquilo inferior o alquilo inferior sustituido con flúor;

siempre y cuando, sin embargo, el compuesto no sea



[0012] En una modalidad, un compuesto de la Fórmula II tiene una estructura de acuerdo con la siguiente estructura sub-genérica, Fórmula IIa,



Fórmula IIa,

todas las sales, profármacos, tautómeros, e isómeros del mismo,

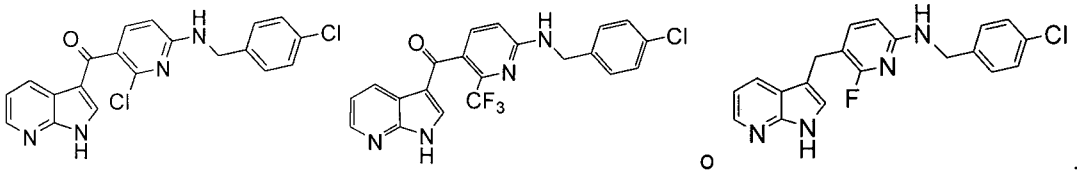
en donde:

Q^{1a} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$;

Q^5 es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

A_2, M_4, Q^{12}, Q^{13}, Q^{14} y R^{41} son como se define para la Fórmula II;

siempre y cuando, sin embargo, el compuesto no sea



o

[0013] En una modalidad de los compuestos de la Fórmula IIa, A_2 es $-CH_2-$ y M_4 es $-NHCH_2-$. En una modalidad A_2 es -C(O)- y M_4 es $-NHCH_2-$. En una modalidad A_2 es -C(O)- y M_4 es -NHC(O)-. En una modalidad A_2 es $-CH_2-$ y M_4 es -NHC(O)-.

[0014] En una modalidad de los compuestos de la Fórmula IIa, A_2 es $-CH_2-$, M_4 es $-NHCH_2-$, Q^5 es $-OR^{41}$, -CN, alquilo C_{1-3}, alquilo C_{1-3} sustituido con flúor, flúor, cloro, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y Q^{13} y Q^{14} son hidrógeno.

[0015] En una modalidad de los compuestos de la Fórmula IIa, A_2 es -C(O)-, M_4 es $-NHCH_2-$, Q^5 es $-OR^{41}$, -CN, alquilo C_{1-3}, alquilo C_{1-3} sustituido con flúor, flúor, cloro, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y Q^{13} y Q^{14} son hidrógeno.

[0016] En una modalidad de los compuestos de la Fórmula IIa, A_2 es -C(O)-, M_4 es -NHC(O)-, Q^5 es $-OR^{41}$, -CN, alquilo C_{1-3}, alquilo C_{1-3} sustituido con flúor, flúor, cloro, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del

grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y Q^{13} y Q^{14} son hidrógeno.

[0017] En una modalidad de los compuestos de la Fórmula IIa, A_2 es $-CH_2-$, M_4 es -NHC(O)-, Q^5 es $-OR^{41}$, -CN, alquilo C_{1-3}, alquilo C_{1-3} sustituido con flúor, flúor, cloro, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y Q^{13} y Q^{14} son hidrógeno.

[0018] En una modalidad, además de cualquiera de las modalidades de la Fórmula IIa anteriormente, R^{41} es R^{42}.

[0019] En una modalidad, además de cualquiera de las modalidades de la Fórmula IIa anteriormente, Q^{1a} es fenilo o piridinilo, en donde el fenilo o piridinilo se sustituyen con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, metilo, metoxi, trifluorometilo, difluorometoxi y trifluorometoxi; A_2 es $-CH_2-$; M_4 es $-NHCH_2-$; y Q^5 es -CN, flúor, cloro, metilo, trifluorometilo, metoxi, difluorometoxi, trifluorometoxi, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor. En una modalidad, además de cualquiera de las modalidades de la Fórmula IIa anteriormente, Q^{1a} es fenilo mono sustituido con cloro, preferiblemente en la posición 4, A_2 es $-CH_2-$; M_4 es $-NHCH_2-$; y Q^5 es -CN, flúor, cloro, metilo, trifluorometilo, metoxi, difluorometoxi, trifluorometoxi, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor. En una modalidad, además de cualquiera de las modalidades de la Fórmula IIa, Q^{1a} es piridin-3-ilo monosustituido con metilo, metoxi, trifluorometilo, difluorometoxi o trifluorometoxi, preferiblemente en la posición 6; A_2 es $-CH_2-$; M_4 es $-NHCH_2-$; Q^5 es -CN, flúor, cloro, metilo, trifluorometilo, metoxi, difluorometoxi, trifluorometoxi, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor.

[0020] En una modalidad de los compuestos de la Fórmula IIa, A_2 es $-CH_2-$; M_4 es $-NHCH_2-$; Q^{1a} es

fenilo o piridinilo, en donde el fenilo o piridinilo se sustituyen con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, metilo, metoxi, trifluorometilo, difluorometoxi y trifluorometoxi; Q^5 es hidrógeno, flúor, cloro, metilo, metoxi, trifluorometilo, difluorometoxi, trifluorometoxi, -CN, o 1-metil-1H-pirazol-4-ilo; Q^{12} es flúor o cloro; y Q^{13} y Q^{14} son hidrógeno. En una modalidad, A_2 es -CH_2-; M_4 es -$NHCH_2$-; Q^{1a} es fenilo mono sustituido con cloro, preferiblemente en la posición 4; Q^5 es hidrógeno, cloro, metilo, metoxi, o -CN; Q^{12} es flúor o cloro; y Q^{13} y Q^{14} son hidrógeno. En una modalidad, A_2 es -CH_2-; M_4 es -$NHCH_2$-; Q^{1a} es piridin-3-ilo monosustituido con metilo, metoxi, trifluorometilo, difluorometoxi o trifluorometoxi, preferiblemente en la posición 6; Q^5 es hidrógeno, cloro, metilo, metoxi, -CN, o 1-metil-1H-pirazol-4-ilo; Q^{12} es flúor o cloro; y Q^{13} y Q^{14} son hidrógeno.

[0021] En una modalidad de los compuestos de la Fórmula IIa, el compuesto se selecciona del grupo que consiste de:

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina **(P-0132)**,

(4-Cloro-bencil)-[6-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0161)**,

[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]piridina-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)**,

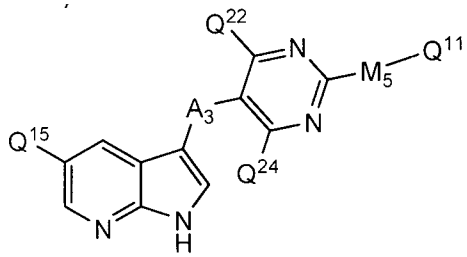
[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0234)**,

[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)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0022] En una modalidad, un compuesto de la Fórmula II tiene una estructura de acuerdo con la siguiente estructura sub-genérica, Fórmula IIb,



Fórmula IIb,

todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

A_3 es $-CH_2-$ o -C(O)-;

Q^{15} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

M_5, Q^{11}, Q^{22}, Q^{24}, y R^{41}, son como se define para la Fórmula II.

[0023] En una modalidad de los compuestos de la Fórmula IIb, M_5 es $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$ o $-NR^{39}C(O)-$; A_3 es $-CH_2-$ o -C(O)-, preferiblemente $-CH_2-$; Q^{11} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; Q^{15} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior,

alcoxi inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; y Q^{22} y Q^{24} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor, preferiblemente hidrógeno, flúor, cloro, o $-CF_3$, más preferiblemente Q^{22} y Q^{24} son hidrógeno; en donde R^{42} es como se define para la Fórmula II.

[0024] En una modalidad de los compuestos de la Fórmula IIb, M_5 es $-NHCH_2-$; A_3 es $-CH_2-$; Q^{11} es fenilo o heteroarilo, en donde el fenilo o heteroarilo se sustituye opcionalmente con 1 o 2 sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; Q^{15} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, y alcoxi inferior sustituido con flúor; y Q^{22} y Q^{24} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor, preferiblemente hidrógeno, flúor, cloro, o $-CF_3$, más preferiblemente Q^{22} y Q^{24} son hidrógeno.

[0025] En una modalidad de los compuestos de la Fórmula IIb, M_5 es $-NHCH_2-$; A_3 es $-CH_2-$; Q^{11} es fenilo sustituido con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, metilo, metilo sustituido con flúor, metoxi, y metoxi sustituido con flúor; Q^{15} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, preferiblemente hidrógeno o cloro; y Q^{22} y Q^{24} son hidrógeno.

[0026] En una modalidad de los compuestos de la Fórmula IIb, el compuesto se selecciona del grupo que consiste de:

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0260)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,6-difluoro-bencil)-amina **(P-0261)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina **(P-0262)**,

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0263)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-bencil)-amina **(P-0264)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,4-difluoro-bencil)-amina **(P-0265)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina **(P-0266)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,5-difluoro-bencil)-amina **(P-0267)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometil-bencil)-amina **(P-0268)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-5-trifluorometil-bencil)-amina **(P-0289)**,

(2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0291)**,

(2,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0292)**,

(2-Cloro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0293)**,

(3-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0294)**,

(3,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0295)**,

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0300)**,

(2-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0301)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina **(P-0302)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina **(P-0303)**,

(5-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0304)**,

(2,4-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0305)**,

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0306)**,

(4-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0307)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina **(P-0308)**,

(2-fluoro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0309)**,

(2,5-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0310)**,

(3-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0311)**,

(2-Difluorometoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0312)**,

(2,3-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0313)**,

(4-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0314)**,

(5-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0315)**,

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0316)**,

(5-Cloro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0317)**,

(5-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0318)**,

(2-fluoro-4-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0319)**,

(4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0320)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-difluorometoxi-bencil)-amina **(P-0390)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-trifluorometil-bencil)-amina **(P-0391)**,

(3-Cloro-2-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0392)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-3-trifluorometil-bencil)-amina **(P-0393)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-4-trifluorometil-bencil)-amina **(P-0394)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,3-difluoro-bencil)-amina **(P-0395)**,

(2-Cloro-4-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0396)**,

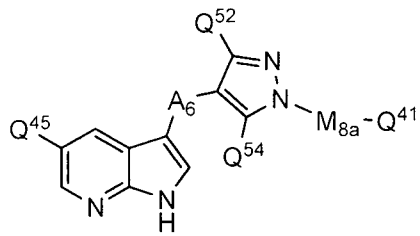
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina **(P-0402)**,

(2-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0407)**,

(2-Cloro-5-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **(P-0408)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0027] En una modalidad, un compuesto de la Fórmula II tiene una estructura de acuerdo con la siguiente estructura sub-genérica, Fórmula IIe,



Fórmula IIe,

todas las sales, profármacos, tautómeros, e isómeros del mismo,

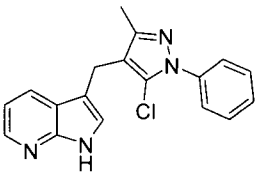
en donde:

A_6 es $-CH_2-$ o $-C(O)-$;

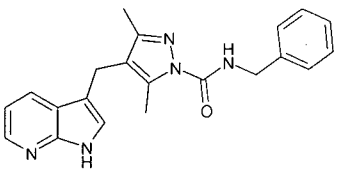
M_{8a} es $-CH_2-$, $-CH_2C(O)-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(R^{40})-$, o $-C(O)NR^{39}CH_2CH_2-$;

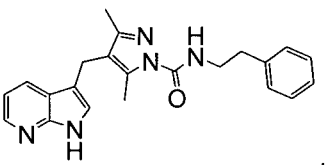
Q^{45} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

Q^{41}, Q^{52}, Q^{54}, R^{39}, R^{40}, y R^{41} son como se define para la Fórmula II;

siempre y cuando, sin embargo, el compuesto no sea 

,



, o 

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[0028] En una modalidad de los compuestos de la Fórmula IIe, M_{8a} es $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, o $-C(O)NR^{39}(CH_2)_2-$; A_6 es $-CH_2-$ o $-C(O)-$, preferiblemente $-CH_2-$; Q^{41} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; Q^{45} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; y Q^{52} y Q^{54} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor, preferiblemente Q^{52} y Q^{54} son independientemente hidrógeno, flúor, cloro, metilo, o $-CF_3$; en donde R^{42} es como se define en la Fórmula II.

[0029] En una modalidad de los compuestos de la Fórmula IIe, M_{8a} es $-C(O)NHCH_2-$, $-C(O)NHCH(CH_3)-$ o $-C(O)NH(CH_2)_2-$; A_6 es $-CH_2-$ o -C(O)-, preferiblemente $-CH_2-$; Q^{41} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, metilo, metilo sustituido con flúor, metoxi, y metoxi sustituido con flúor; Q^{45} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor, preferiblemente hidrógeno o cloro; y Q^{52} y Q^{54} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor, preferiblemente Q^{52} y Q^{54} son metilo.

[0030] En una modalidad de los compuestos de la Fórmula IIe, el compuesto se selecciona del grupo que consiste de:

3-(1-Bencil-3,5-dimetil-1H-pirazol-4-ilmetil)-1H-pirrolo[2,3-b]piridina **(P-0133)**,

2-[3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-il]-1-fenil-etanona **(P-0134)**,

4-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0135)**,

2-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0136)**,

2-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0137)**,

3-[3,5-Dimetil-1-(5-trifluorometil-furan-2-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina **(P-0138)**,

3-[3,5-Dimetil-1-(5-metil-isoxazol-3-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina **(P-0139)**,

4-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0140)**,

[2-(4-metoxi-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0141)**,

3-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0142)**,

3-{3,5-Dimetil-1-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetil]-1H-pirazol-4-ilmetil}-1H-pirrolo[2,3-

b]piridina **(P-0143)**,

3-[3,5-Dimetil-1-(4-metil-2-fenil-tiazol-5-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina **(P-0144)**,

2-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0145)**,

[2-(2,4-dicloro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0146)**,

[2-(4-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0147)**,

[2-(2-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0148)**,

((S)-1-fenil-etil)-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0149)**,

3-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0150)**,

4-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0151)**,

4-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0152)**,

2-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **(P-0153)**,

[2-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico **(P-0157)**,

4-fluoro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico **(P-0158)**,

4-cloro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico **(P-0159)**,

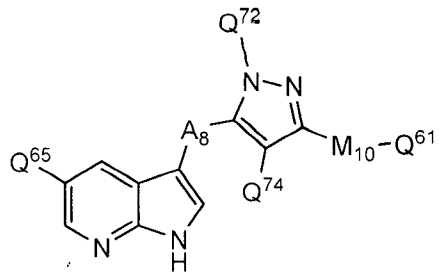
[(S)-1-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-

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pirazol-1-carboxílico **(P-0160)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0031] En una modalidad, un compuesto de la Fórmula II tiene una estructura de acuerdo con la siguiente estructura sub-genérica, Fórmula IIg,



Fórmula IIg,

todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

A_8 es $-CH_2-$, o $-C(O)-$;

Q^{65} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

M_{10}, Q^{61}, Q^{72}, Q^{74}, y R^{41} son como se define para la Fórmula II.

[0032] En una modalidad de los compuestos de la Fórmula IIg, M_{10} es $-NR^{39}CH_2-$ o $-NR^{39}-(CH_2)_2-$; A_8 es $-CH_2-$ o $-C(O)-$, preferiblemente $-CH_2-$; Q^{61} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; Q^{65} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; y Q^{74} es hidrógeno, flúor, cloro, alquilo inferior o

alquilo inferior sustituido con flúor, en donde R^{42} es como se define para la Fórmula II.

[0033] En una modalidad de los compuestos de la Fórmula IIg, M_{10} es $-NHCH_2-$; A_8 es $-CH_2-$; Q^{61} es fenilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, metilo, trifluorometilo, metoxi, difluorometoxi o trifluorometoxi; Q^{65} es hidrógeno, flúor, -CN, o 1-metil-pirazol-4-ilo; Q^{72} es alquilo inferior o alquilo inferior sustituido con flúor; y Q^{74} es hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor. En una modalidad, M_{10} es $-NHCH_2-$; A_8 es $-CH_2-$; Q^{61} es 4-fluoro-fenilo; Q^{65} es hidrógeno, cloro, -CN, o 1-metil-pirazol-4-ilo; Q^{72} es metilo o etilo; y Q^{74} es hidrógeno o cloro.

[0034] En una modalidad, el compuesto de la Fórmula IIg se selecciona del grupo que consiste de:

[1-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **(P-0165)**,

(4-fluoro-bencil)-[1-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-amina **(P-0169)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **(P-0170)**,

(4-fluoro-bencil)-{1-metil-5-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-1H-pirazol-3-il}-amina **(P-0180)**,

(5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-[2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-il]-metanona **(P-0184)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-etil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **(P-0185)**,

3-[5-(4-fluoro-bencilamino)-2-metil-2H-pirazol-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0191)**,

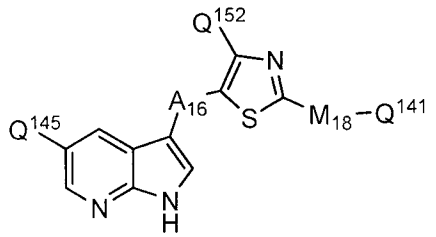
(3-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina **(P-0410)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(2,5-difluoro-bencil)-amina **(P-0411)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0035] En una modalidad, un compuesto de la Fórmula II tiene una estructura de acuerdo con la siguiente estructura sub-genérica, Fórmula IIp,

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Fórmula IIp,

todas las sales, profármacos, tautómeros, e isómeros del mismo,

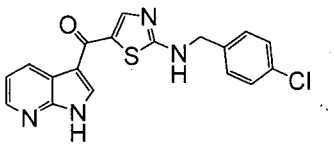
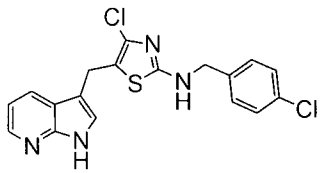
en donde:

A_{16} es $-CH_2-$ o -C(O)-;

Q^{145} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$;

Q^{152} es hidrógeno, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor; y

M_{18}, Q^{141}, y R^{41}, son como se define para la Fórmula II;

siempre y cuando, sin embargo, el compuesto no sea  o 

[0036] En una modalidad de los compuestos de la Fórmula IIp, M_{18} es $-NR^{39}CH_2-$ o $-NR^{39}-(CH_2)_2-$; A_{16} es $-CH_2-$ o -C(O)-, preferiblemente $-CH_2-$; Q^{141} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$;

Q^{145} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{42}$, $-NR^{42}R^{42}$, y $-OR^{42}$; y Q^{152} es hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor; en donde R^{42} es como se define para la Fórmula II.

[0037] En una modalidad de los compuestos de la Fórmula IIp, M_{18} es $-NH-CH_2-$ o $-NH-(CH_2)_2-$, preferiblemente $-NH-CH_2-$; A_{16} es $-CH_2-$ o -C(O)-, preferiblemente $-CH_2-$; Q^{141} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con 1 o 2 sustituyentes seleccionados del grupo que consiste de flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, y heterocicloalquilo; Q^{145} es hidrógeno, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor, preferiblemente hidrógeno, -CN, o cloro; y Q^{152} es hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor, preferiblemente hidrógeno o cloro, más preferiblemente cloro.

[0038] En una modalidad, el compuesto de la Fórmula Ih se selecciona del grupo que consiste de [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **(P-0156)**, [4-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **(P-0162)**, (4-fluoro-bencil)-[4-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **(P-0163)**, [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]-piridin-2-ilmetil-amina **(P-0167)**, [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina **(P-0168)**, [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina **(P-0171)**, [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1,5-dimetil-1H-pirazol-3-ilmetil)-amina **(P-0172)**, [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **(P-0173)**, [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-2H-pirazol-3-ilmetil)-amina **(P-0175)**,

[2-(4-fluoro-bencilamino)-tiazol-5-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **(P-0177)**,

{2-[(4-Cloro-bencil)-metil-amino]-tiazol-5-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **(P-0178)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-tiazol-2-ilmetil-amina **(P-0189)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **(P-0190)**,

Bencil-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **(P-0192)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-metoxi-bencil)-amina **(P-0193)**,

(4-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **(P-0194)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **(P-0195)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina **(P-0196)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina **(P-0197)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-2H-pirazol-3-ilmetil)-amina **(P-0198)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina **(P-0199)**,

[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]-(2-metil-tiazol-4-ilmetil)-amina **(P-0201)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-metil-tiazol-5-ilmetil)-amina **(P-0202)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-cloro-piridin-2-ilmetil)-amina **(P-0203)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina **(P-0204)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina **(P-0205)**,

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[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina **(P-0206)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina **(P-0207)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4,5-dimetil-tiofen-2-ilmetil)-amina **(P-0208)**,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-tiofen-3-ilmetil)-amina **(P-0209)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **(P-0231)**,

[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]-piridin-4-ilmetil-amina **(P-0237)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-cloro-piridin-4-ilmetil)-amina **(P-0238)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1-etil-1H-pirazol-4-ilmetil)-amina **(P-0239)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina **(P-0240)**,

[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-cloro-6-fluoro-bencil)-amina **(P-0243)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-fenetil-amina **(P-0244)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-difluoro-bencil)-amina **(P-0245)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-fluoro-bencil)-amina **(P-0246)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina **(P-0247)**,

(2-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **(P-0248)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-bencil)-amina **(P-0249)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-cloro-4-fluoro-bencil)-amina **(P-**

240

0250),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-2-ilmetil)-amina **(P-0251)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina **(P-0252)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3,5-dicloro-piridin-4-ilmetil)-amina **(P-0253)**,

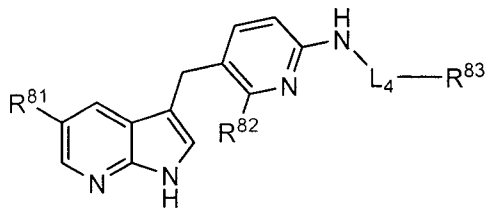
[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-trifluorometil-bencil)-amina **(P-0254)**,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina **(P-0255)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **(P-0290)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0039] Los compuestos de la Fórmula III tienen la siguiente estructura:



Fórmula III,

todas las sales, profármacos, tautómeros, e isómeros de los mismos,

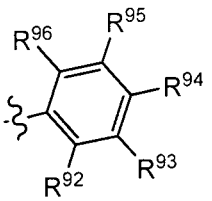
en donde:

L_4 es $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, -C(O)- o -C(O)NH-;

R^{81} se selecciona del grupo que consiste de hidrógeno, $-OR^{41}$, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$;

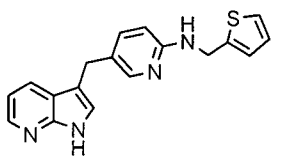
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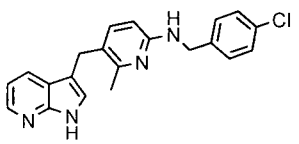
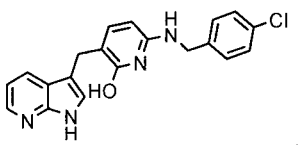
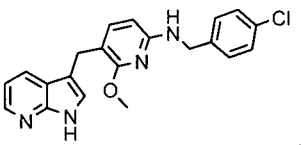
R^{82} se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-3}, alquilo C_{2-3} sustituido con flúor, OH, alcoxi C_{1-3}, y alcoxi C_{1-3} sustituido con flúor;

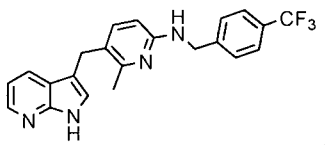
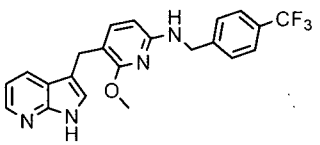
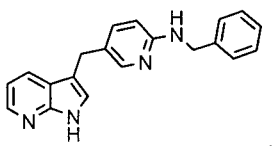
R^{83} es heterocicloalquilo, heteroarilo, o  , en el cual  indica el punto de unión de R^{83} a L_4 de la Fórmula III, en donde el heterocicloalquilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$;

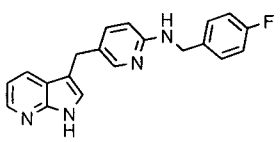
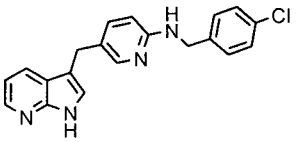
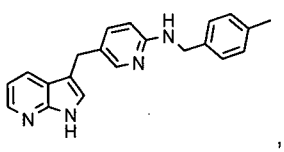
R^{92}, R^{93}, R^{94}, R^{95}, y R^{96} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$; y

R^{40} y R^{41} son como se define para la Fórmula II;

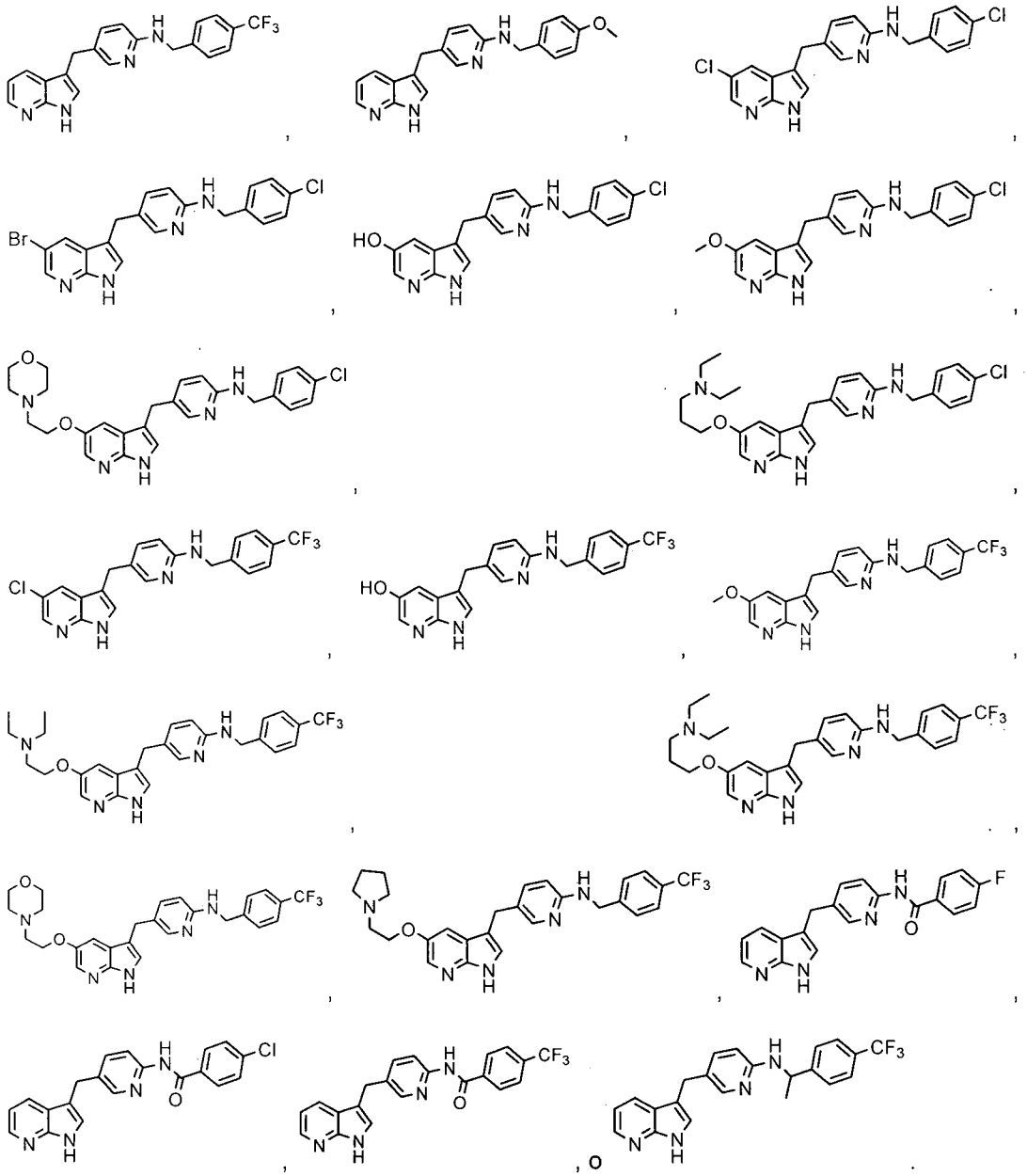
siempre y cuando, sin embargo, el compuesto no sea  ,

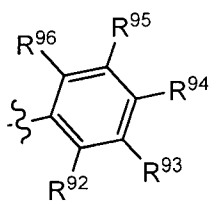
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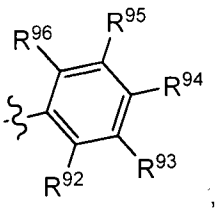
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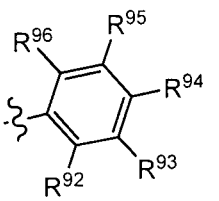
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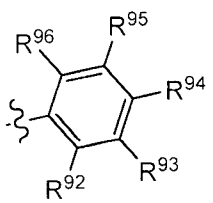


[0040] En una modalidad de los compuestos de la Fórmula III, L_4 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o -C(O)-; R^{81} es hidrógeno, flúor, cloro, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor; R^{82} es hidrógeno; R^{83} es  , en donde R^{92}, R^{93}, R^{94}, R^{95}, y R^{96} son independientemente hidrógeno, flúor, cloro, alquilo inferior, alquilo

inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor, siempre y cuando, sin embargo, cuando R^{94} sea flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor, al menos uno de R^{92}, R^{93}, R^{95}, y R^{96} sea flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor.

[0041] En una modalidad de los compuestos de la Fórmula III, L_4 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o $-C(O)-$; R^{81} es hidrógeno, flúor, cloro, -CN, metilo, o metoxi, preferiblemente hidrógeno, cloro, -CN, o metilo; R^{82} es hidrógeno; R^{83} es  , en donde R^{92}, R^{93}, R^{94}, R^{95}, y R^{96} son independientemente hidrógeno, flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi o trifluorometoxi, preferiblemente hidrógeno, cloro, metilo, trifluorometilo, metoxi, etoxi, o trifluorometoxi, siempre y cuando, sin embargo, cuando R^{94} sea flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi o trifluorometoxi, al menos uno de R^{92}, R^{93}, R^{95}, y R^{96} sea flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi o trifluorometoxi.

[0042] En una modalidad de los compuestos de la Fórmula III, L_4 es $-CH_2-$; R^{81} es flúor, cloro, -CN, metilo, o metoxi, preferiblemente cloro, -CN, o metilo; R^{82} es hidrógeno; R^{83} es  , en donde R^{94} es hidrógeno y R^{92}, R^{93}, R^{95}, y R^{96} son independientemente hidrógeno, flúor, cloro, metilo, trifluorometilo, metoxi, etoxi, difluorometoxi o trifluorometoxi.

[0043] En una modalidad de los compuestos de la Fórmula III, L_4 es $-CH_2-$, $-CH_2CH_2-$, $-C(O)-$, o $-CH(CH_3)-$, preferiblemente $-CH_2-$ o $-C(O)-$; R^{81} es hidrógeno o flúor; R^{82} es hidrógeno; R^{83} es  , en donde R^{92} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi,

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difluorometoxi, o trifluorometoxi, preferiblemente flúor, cloro, metilo, o trifluorometilo, y en donde R^{93}, R^{94}, R^{95}, y R^{96} son independientemente hidrógeno, flúor, cloro, metilo, trifluorometilo, metoxi, difluorometoxi o trifluorometoxi, preferiblemente hidrógeno o flúor. En una modalidad, L_4 es $-CH_2-$, -C(O)-, o $-CH(CH_3)-$; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, metilo, o trifluorometilo; y R^{93}, R^{94}, R^{95}, y R^{96} son hidrógeno. En una modalidad, L_4 es $-CH_2-$, -C(O)-, o $-CH(CH_3)-$; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, metilo, o trifluorometilo; R^{94}, R^{95}, y R^{96} son hidrógeno; y R^{93} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, cloro, trifluorometilo o metoxi, más preferiblemente flúor. En una modalidad, L_4 es $-CH_2-$, -C(O)-, o $-CH(CH_3)-$; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, metilo, o trifluorometilo; R^{93}, R^{95}, y R^{96} son hidrógeno; y R^{94} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, cloro, metilo o trifluorometilo, más preferiblemente flúor. En una modalidad, L_4 es $-CH_2CH_2-$ o -C(O)-; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92}, R^{95}, y R^{96} son hidrógeno; R^{93} es hidrógeno, flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente hidrógeno, flúor, cloro, metilo, trifluorometilo, metoxi, o trifluorometoxi más preferiblemente flúor, cloro, trifluorometilo o metoxi; y R^{94} es hidrógeno, flúor, o cloro; siempre y cuando, sin embargo, cuando L_4 sea -C(O)- y R^{94} sea flúor o cloro, R^{93} no sea hidrógeno. En una modalidad, L_4 es $-CH_2CH_2-$; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92}, R^{94}, R^{95}, y R^{96} son hidrógeno; y R^{93} es hidrógeno, flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente hidrógeno o flúor. En una modalidad, L_4 es -C(O)-; R^{81} es hidrógeno; R^{82} es hidrógeno; R^{92}, R^{95}, y R^{96} son hidrógeno; R^{93} es flúor, cloro, metilo, etilo, trifluorometilo, metoxi, etoxi, difluorometoxi, o trifluorometoxi, preferiblemente flúor, cloro, trifluorometilo o metoxi; y R^{94} es hidrógeno, flúor, o cloro.

[0044] En una modalidad de los compuestos de la Fórmula III, R^{83} es pirrolidina, morfolina, piridina, pirimidina, pirazina, pirazol, isoxazol, imidazol, o bencimidazol, en donde R^{83} se sustituye

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opcionalmente con uno o más sustituyentes independientemente seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$, preferiblemente en donde R^{83} se sustituye opcionalmente con 1 o 2 sustituyentes independientemente seleccionados de flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, o cicloalquilamino, más preferiblemente flúor, cloro, metilo, trifluorometilo, metoxi o morfolina.

[0045] En una modalidad de los compuestos de la Fórmula III, L_4 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o -C(O)-, preferiblemente $-CH_2-$, $-CH_2CH_2-$, o -C(O)-; R^{81} es hidrógeno, flúor, cloro, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, o alcoxi inferior sustituido con flúor, preferiblemente hidrógeno, cloro, metilo o -CN; R^{82} es hidrógeno; y R^{83} es pirrolidina, morfolina, piridina, pirimidina, pirazina, pirazol, isoxazol, imidazol, o bencimidazol, en donde R^{83} se sustituye opcionalmente con 1 o 2 sustituyentes independientemente seleccionados de flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, o cicloalquilamino, preferiblemente flúor, cloro, metilo, trifluorometilo, metoxi o morfolina.

[0046] En una modalidad de los compuestos de la Fórmula III, el compuesto se selecciona del grupo que consiste de:

Piridin-3-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0094)**,

(5-Metil-isoxazol-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0095)**,

(2-Pirrolidin-1-il-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0096)**,

[1-(4-Metanosulfonil-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0097)**,

(2-Morfolin-4-il-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0099)**,

3,4-Dicloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0100)**,

2-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0101)**,

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido 2,5-Dimetil-2H-pirazol-3-carboxílico **(P-0102)**,

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido tiofeno-2-carboxílico **(P-0103)**,

2-Metoxi-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida **(P-0104)**,

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida **(P-0105)**,

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[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido pirazina-2-carboxílico **(P-0106)**,

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido piridina-2-carboxílico **(P-0107)**,

6-Metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-nicotinamida **(P-0108)**,

4-fluoro-3-metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0109)**,

5-Metil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido pirazina-2-carboxílico **(P-0110)**,

3-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0111)**,

4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida **(P-0112)**,

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometoxi-benzamida **(P-0113)**,

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida **(P-0114)**,

3-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0115)**,

3,4-Difluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0116)**,

2-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0117)**,

5-fluoro-2-metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0118)**,

2-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0119)**,

3-Metoxi-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0120)**,

3-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0121)**,

3-Metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **(P-0122)**,

2-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida **(P-0123)**,

((R)-1-Fenil-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0125)**,

(3-Morfolin-4-il-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0126)**,

[1-(2-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0127)**,

[2-(3-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0128)**,

(3-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0129)**,

(1-Metil-1H-imidazol-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0130)**,

(1,5-Dimetil-1H-pirazol-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0131)**,

[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)**,

(3-Cloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0183)**,

(2-Cloro-6-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0210)**,

Fenetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0211),**

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0212)**,

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0213)**,

(3-Bromo-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0214)**,

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0215)**,

(2-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0216)**,

(2-Metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0217)**,

(1-Metil-1H-benzoimidazol-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0218)**,

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0219)**,

(1H-Benzoimidazol-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0220)**,

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0221)**,

(5-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0222)**,

(3-fluoro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0223)**,

(6-Metoxi-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0224)**,

(4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0225)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina **(P-0226)**,

(3,5-Dicloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0227)**,

(6-Morfolin-4-il-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0228)**,

(3-fluoro-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0229)**,

(5-fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0230)**,

(3-Cloro-piridin-4-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0235)**,

3-{6-[(3-Cloro-piridin-4-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0256)**,

3-[6-(4-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0257)**,

(2,4-difluoro-3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido

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propano-1-sulfónico **(P-0258)**,

(3-{[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-2,4-difluoro-fenil)-amida del ácido propano-1-sulfónico **(P-0259)**,

3-[6-(4-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0269)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-bencil)-amina **(P-0270)**,

3-[6-(2-fluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0271)**,

(2-fluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0272)**,

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0273)**,

3-[6-(2-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0274)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina **(P-0275)**,

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina **(P-0276)**,

3-[6-(2,6-Difluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0277)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-difluoro-bencil)-amina **(P-0278)**,

(2-Cloro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0279)**,

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0280)**,

3-[6-(2-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0281)**,

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0282)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **(P-0283)**,

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-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]piridina-5-carbonitrilo **(P-0287)**,

(2-Etoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0288)**,

(2,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0296)**,

(2,5-Difluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0297)**,

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[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,5-difluoro-bencil)-amina **(P-0298)**,

3-[6-(2,5-Difluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0299)**,

3-[6-(2-Trifluorometoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0321)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometoxi-bencil)-amina **(P-0322)**,

3-[6-(2-Etoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0323)**,

[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]-(2-trifluorometil-bencil)-amina **(P-0325)**,

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina **(P-0326)**,

(2-Cloro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0327)**,

(2-Cloro-bencil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0328)**,

(2,5-Difluoro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0329)**,

(2,5-Difluoro-bencil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0330)**,

[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)**,

(2,6-Difluoro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0333)**,

(2,6-Difluoro-bencil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0334)**,

(2-Metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0336)**,

3-[6-(2-Metoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0337)**,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-difluorometoxi-bencil)-amina **(P-0338)**,

3-[6-(2-Difluorometoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **(P-0339)**,

(2,6-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0340)**,

(2,6-Difluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0341)**,

(2,4-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0342)**,

(3-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0343)**,

(2-fluoro-4-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0344)**,

(4-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0345)**,

(3-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0346)**,

(2-Morfolin-4-il-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0347)**,

(4-Cloro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0348)**,

(2-Cloro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0349)**,

(2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0350)**,

(2,3-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0351)**,

(2-fluoro-3-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0352)**,

Dimetil-(5-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-amina **(P-0353)**,

(3-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0354)**,

(5-fluoro-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0355)**,

(3,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0356)**,

(2-Propoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0357)**,

(2-Morfolin-4-il-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0358)**,

(2-Cloro-3-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0359)**,

(2-fluoro-6-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0360)**,

[2-(2-Morfolin-4-il-etoxi)-bencil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0361)**,

(2,3-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0362)**,

(2-Cloro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0363)**,

(2-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0364)**,

(2-fluoro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0365)**,

(5-fluoro-2-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0366)**,

(2-Difluorometoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0367)**,

(2-fluoro-4-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0368)**,

[2-(3-Dimetilamino-propoxi)-bencil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0369)**,

(2,6-Dimetoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0370)**,

(2-fluoro-5-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0371)**,

(4-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0372)**,

(3-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0373)**,

(6-Ciclopentiloxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0374)**,

(5-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0375)**,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina **(P-0376)**,

(2-fluoro-3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido propano-1-sulfónico **(P-0377)**,

(2,5-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0380)**,

Pirimidin-5-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0381)**,

(5-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0382)**,

(2-Etil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0383)**,

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)**,

Metil-(5-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-amina **(P-0386)**,

(2-Cloro-4-metanosulfonil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0387)**,

Posiblemente para agregarse (P-0388),

(5-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0397)**,

Dimetil-(3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-il)-amina **(P-0399)**,

(5-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0400)**,

(2-Metoxi-pirimidin-5-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0401)**,

[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)**,

1-(3-fluoro-fenil)-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-urea **(P-0412)**, y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0047] En una modalidad, un compuesto de la invención es:

(4-Cloro-bencil)-[6-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridazin-3-il]-amina **(P-0092),**

(4-Morfolin-4-ilmetil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0093)**,

(2-Metoxi-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0098)**,

[4-Cloro-1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-[1-(4-fluoro-fenil)-met-(E)-ilideno]-amina **(P-0166)**,

((2,2-Difluoro-benzo[1,3]dioxol-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **(P-0398)**; o

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

[0048] En ciertas modalidades de los compuestos anteriores, se excluyen compuestos donde N (excepto donde N es un átomo de anillo heteroarilo), O, o S se une a un carbono que también se une a N (excepto donde N es un átomo de anillo heteroarilo), O, o S, excepto donde el carbono forma un doble enlace con uno de los heteroátomos, tal como en una amida, ácido carboxílico, y similares; o donde N (excepto donde N es un átomo de anillo heteroarilo), O, C(S), C(O), o $S(O)_n$ (n es 0-2) se une a un carbono de alqueno de un grupo alquenilo o se une a un carbono de alquino de un grupo alquinilo; por consiguiente, en ciertas modalidades los compuestos que incluyen enlaces tales como los siguientes se excluyen de la presente invención: -NR-CH_2-NR-, -O-CH_2-NR-, -S-CH_2-NR-, -NR-CH_2-O-, –O-CH_2-O-, -S-CH_2-O-,–NR-CH_2-S-, –O-CH_2-S-, –S-CH_2-S-, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, -$S(O)_{0-2}$-CH=CH-, -CH=CH-$S(O)_{0-2}$-, –$S(O)_{0-2}$-C≡C-, -C≡C-$S(O)_{0-2}$-, –C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, o -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, o -C(S)-C≡C-.

[0049] En referencia a los compuestos en este documento, la especificación de un compuesto o grupo de compuestos incluye sales farmacéuticamente aceptables de tal o tales compuestos, profármaco o profármacos, y todos los estereoisómeros, a menos que se indique claramente lo contrario. En referencia a los compuestos de la Fórmula II, se entiende que tal referencia incluye compuestos de las Fórmulas IIa, IIb, IIe, IIg y IIp, y todas las sub-modalidades de los mismos.

[0050] En otro aspecto, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por c-kit en un sujeto animal (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tales 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 c-kit (por ejemplo, actividad de cinasa). Los métodos de la invención implican administrar, al sujeto que adolece o

está en riesgo de una enfermedad o padecimiento mediado por c-kit, una cantidad efectiva de un compuesto de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos. En una modalidad, la enfermedad mediada por c-kit se selecciona del grupo que consiste de malignidades, incluyendo tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal (GISTs), glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mielocítica aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mastocitosis, melanoma, y tumores de mastocitos caninos, y enfermedades inflamatorias, incluyendo asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, e hipereosinofilia.

[0051] En un aspecto relacionado, los compuestos de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por c-kit seleccionado del grupo que consiste de malignidades, incluyendo tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal (GISTs), glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mielocítica aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mastocitosis, melanoma, y tumores de mastocitos caninos, y enfermedades inflamatorias, incluyendo asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, e hipereosinofilia.

[0052] En un aspecto adicional, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por c-fms en un sujeto animal (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tales 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 c-fms (por ejemplo, actividad de cinasa). Los métodos de la invención implican administrar al sujeto que

adolece o está en riesgo de una enfermedad o padecimiento mediado por c-fms una cantidad efectiva del compuesto de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos. En una modalidad, la enfermedad mediada por c-fms se selecciona del grupo que consiste de trastornos inmunes, incluyendo artritis reumatoide, lupus eritematoso sistémico (SLE), y rechazo de transplantes; enfermedades inflamatorias incluyendo síndrome inflamatorio intestinal, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica (COPD), enfisema, y ateroesclerosis; trastornos metabólicos, incluyendo Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, y metástasis de cáncer a hueso; enfermedades renales, incluyendo nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia; trastornos del sistema nervioso central, incluyendo esclerosis múltiple, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson; dolor inflamatorio y crónico, incluyendo dolor óseo; y cánceres, incluyendo mieloma múltiple, leucemia mieloide aguda, leucemia mieloide crónica (CML), cáncer de próstata, cáncer de mama, cáncer ovárico, y metástasis de tumores a otros tejidos.

[0053] En un aspecto relacionado, los compuestos de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por c-fms seleccionado del grupo que consiste de trastornos inmunes, incluyendo artritis reumatoide, lupus eritematoso sistémico (SLE), y rechazo de transplantes; enfermedades inflamatorias incluyendo síndrome inflamatorio intestinal, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica (COPD), enfisema, y ateroesclerosis; trastornos metabólicos, incluyendo Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, y metástasis de cáncer a hueso; enfermedades renales, incluyendo nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia;

trastornos del sistema nervioso central, incluyendo esclerosis múltiple, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson; dolor inflamatorio y crónico, incluyendo dolor óseo; y cánceres, incluyendo mieloma múltiple, leucemia mieloide aguda, leucemia mieloide crónica (CML), cáncer de próstata, cáncer de mama, cáncer ovárico, y metástasis de tumores a otros tejidos.

[0054] En un aspecto adicional, la invención proporciona métodos para tratar una enfermedad o padecimiento mediado por c-fms y mediado por c-kit en un sujeto animal (por ejemplo, un mamífero, tal como un humano, otros primates, animales para deporte, animales de interés comercial tales 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 c-fms y actividad de c-kit anormales (por ejemplo, actividad de cinasa). Los métodos de la invención implican administrar al sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por c-fms y mediado por c-kit una cantidad efectiva del compuesto de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos. En una modalidad, la enfermedad mediada por c-fms y c-kit se selecciona del grupo que consiste de tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal, glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mieloma múltiple, mastocitosis, melanoma, cáncer de mama, cáncer ovárico, cáncer de próstata, tumores de mastocitos caninos, metástasis de cáncer a hueso u otros tejidos, hipertrofia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, lupus eritematoso sistémico, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica, enfisema, ateroesclerosis, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, lipólisis, hipereosinofilia, osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia,, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, apoplejía, enfermedad de Alzheimer, enfermedad de Parkinson, dolor inflamatorio, dolor crónico, y dolor óseo.

[0055] En un aspecto relacionado, los compuestos de la Fórmula II o Fórmula III, y todas las sub-modalidades de los mismos, pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por c-fms y mediado por c-kit seleccionado del grupo que consiste de tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal, glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mieloma múltiple, mastocitosis, melanoma, cáncer de mama, cáncer ovárico, cáncer de próstata, tumores de mastocitos caninos, metástasis de cáncer a hueso u otros tejidos, hipertrofia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, lupus eritematoso sistémico, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica, enfisema, ateroesclerosis, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, lipólisis, hipereosinofilia, osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, apoplejía, enfermedad de Alzheimer, enfermedad de Parkinson, dolor inflamatorio, dolor crónico, y dolor óseo.

[0056] En modalidades particulares, el compuesto tiene una IC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, o menos de 5 nM cuando se determina en un ensayo generalmente aceptado de actividad cinasa. En ciertas modalidades, la selectividad del compuesto es tal que el compuesto es al menos 2 veces, 5 veces, 10 veces, o 100 veces más activo sobre c-kit que sobre Ret, PDGF, o tanto Ret como PDGF. En ciertas modalidades, la selectividad del compuesto es tal que el compuesto es al menos 2 veces, 5 veces, 10 veces, o 100 veces más activo sobre c-kit que sobre c-fms. En ciertas modalidades, la selectividad del compuesto es tal que el compuesto es al menos 2 veces, 5 veces, 10 veces, o 100 veces más activo sobre c-fms que sobre c-kit. En ciertas modalidades, el compuesto tiene en combinación cada par de actividad (por ejemplo, IC_{50}) y/o selectividad como se especifica en este párrafo.

[0057] En modalidades particulares, el compuesto tiene una IC_{50} de menos de 100 nM, menos de

50 nM, menos de 20 nM, menos de 10 nM, o menos de 5 nM cuando se determina en un ensayo generalmente aceptado de actividad cinasa para c-kit, c-fms, o actividad de cinasa de c-kit y c-fms. En ciertas modalidades, la selectividad del compuesto es tal que el compuesto es al menos 2 veces, 5 veces, 10 veces, o 100 veces más activo sobre c-kit, c-fms, o tanto c-kit como c-fms que sobre Ret, PDGF, o tanto Ret como PDGF.

[0058] Un aspecto adicional de esta invención se relaciona con composiciones que incluyen una cantidad terapéuticamente efectiva de un compuesto de la Fórmula II o Fórmula III y todas las sub-modalidades de los mismos y al menos un portador, excipiente, y/o diluyente farmacéuticamente aceptable, incluyendo combinaciones de dos cualesquiera o más compuestos de la Fórmula II o Fórmula III. La composición además puede incluir uno o más compuestos diferentes farmacológicamente activos, que pueden incluir uno o más compuestos de la Fórmula II o Fórmula III.

[0059] En un aspecto relacionado, la invención proporciona equipos que incluyen una composición como se describe en este documento. En modalidades particulares, la composición se empaca, por ejemplo, en un vial, botella, frasco, que además puede empacarse, por ejemplo, dentro de una caja, envoltura, o bolsa; la 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; la composición se aprueba para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por c-kit- y/o c-fms; el equipo de la invención incluye instrucciones escritas sobre el uso y/u otra indicación de que la composición es adecuada o está aprobada para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por c-kit- y/o c-fms; la composición se empaca en forma de dosis unitaria o dosis única, por ejemplo, píldoras de dosis única, cápsulas, o similares.

[0060] En otro aspecto, la presente invención también proporciona un método para modular la actividad de c-kit o c-fms al poner en contacto c-kit o c-fms con una cantidad efectiva de un compuesto de la Fórmula II o Fórmula III y todas las sub-modalidades de los mismos activas sobre c-kit y/o c-fms (tales como compuestos desarrollados usando los métodos descritos en este documento). El compuesto se proporciona preferiblemente en un nivel suficiente para modular la

actividad de la c-kit o c-fms por al menos 10%, más preferiblemente al menos 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, o más de 90%. En muchas modalidades, el compuesto estará a una concentración de alrededor de 1 µM, 100 µM, o 1 mM, o en un intervalo de 1-100 nM, 100-500 nM, 500-1000 nM, 1-100 µM, 100-500 µM, o 500-1000 µM. En modalidades particulares, el contacto se lleva a cabo *in vitro*.

[0061] Aspectos y modalidades adicionales serán obvios a partir de la siguiente Descripción Detallada y a partir de las reivindicaciones.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0062] Como se usan en este documento, se aplican las siguientes definiciones:

[0063] "Halo" y "halógeno" se refiere a todos los halógenos, es decir, cloro (Cl), flúor (F), bromo (Br), o yodo (I).

[0064] "Hidroxilo" y "hidroxi" se refiere al grupo -OH.

[0065] "Tiol" se refiere al grupo -SH.

[0066] "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. El grupo alquilo de cadena lineal o ramificado se une en cualquier punto disponible para producir un compuesto estable. En muchas modalidades, un alquilo inferior es un grupo alquilo lineal o ramificado que contiene de 1-6, 1-4, o 1-2, átomos de carbono, tales como metilo, etilo, propilo, isopropilo, butilo, t-butilo, y similares. "Alquilo inferior opcionalmente sustituido" denota alquilo inferior que se sustituye independientemente, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, unidos 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. Aunque se entiende que las sustituciones se unen en cualquier átomo disponible para producir un compuesto estable, cuando el alquilo opcionalmente sustituido es un grupo R de una porción tal como -O, -NHR, -C(O)NHR, y similares, la sustitución del grupo alquilo

R es tal que la sustitución del carbono del alquilo unido a cualquier -O-, -S-, o -N- de la porción (excepto donde -N- es un átomo de anillo heteroarilo) excluye sustituyentes que pueden resultar en cualquier -O-, -S-, o -N- del sustituyente (excepto donde -N- es un átomo de anillo heteroarilo) uniéndose al carbono del alquilo unido a cualquier -O-, -S-, o -N- de la porción.

[0067] "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, tales como ciclopropilo, ciclopentilo, ciclohexilo, adamantilo, y similares. Un "cicloalquilo sustituido" es un cicloalquilo que se sustituye independientemente, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable.

[0068] "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 uno de los carbonos del anillo es oxo sustituido, 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 se retiene un anillo estable. Ejemplos de grupos heterocicloalquilo incluyen, pero no se limitan a, morfolino, tetrahidrofuranilo, dihidropiridinilo, piperidinilo, pirrolidinilo, pirrolidonilo, piperazinilo, dihidrobenzofurilo, y dihidroindolilo. Un "heterocicloalquilo sustituido" es un heterocicloalquilo que se sustituye independientemente, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable.

[0069] "Arilo", solo o en combinación, se refiere a un sistema monocíclico o bicíclico de anillos que contienen hidrocarburos aromáticos tales como fenilo o naftilo, que pueden fusionarse opcionalmente con un cicloalquilo de preferiblemente 5-7, más preferiblemente 5-6, miembros de anillo. Un "arilo sustituido" es un arilo que se sustituye independientemente, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, unidos en cualquier átomo disponible

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para producir un compuesto estable.

[0070] "Heteroarilo", solo o en combinación, se refiere a una estructura de anillos aromáticos, monocíclicos que contiene 5 o 6 átomos de anillo, o un grupo aromático bicíclico que tiene 8 a 10 átomos, que contiene uno o más, preferiblemente 1-4, más preferiblemente 1-3, incluso más preferiblemente 1-2, heteroátomos independientemente seleccionados del grupo que consiste de O, S, y N. Heteroarilo también pretende incluir S o N oxidado, tal como sulfinilo, sulfonilo y N-óxido de un nitrógeno de anillo terciario. Un átomo de carbono o nitrógeno es el punto de unión de la estructura de anillos heteroarilo de tal modo que se produce un compuesto estable. Ejemplos de grupos heteroarilo incluyen, pero no se limitan a, piridinilo, piridazinilo, pirazinilo, quinaoxalilo, indolizinilo, benzo[b]tienilo, quinazolinilo, purinilo, indolilo, quinolinilo, pirimidinilo, pirrolilo, oxazolilo, tiazolilo, tienilo, isoxazolilo, oxatiadiazolilo, isotiazolilo, tetrazolilo, imidazolilo, triazinilo, furanilo, benzofurilo, e indolilo. "Heteroarilo que contiene nitrógeno" se refiere a heteroarilo en donde cualesquier heteroátomos son N. Un "heteroarilo sustituido" es un heteroarilo que se sustituye independientemente, con uno o más, preferiblemente 1, 2, 3, 4 o 5, también 1, 2, o 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable.

[0071] "Alcoxi inferior" denota el grupo $-OR^z$, donde R^z es alquilo inferior. "Alcoxi inferior sustituido" denota alcoxi inferior en el cual R^z es alquilo inferior sustituido con uno o más sustituyentes, como se indica en este documento, unidos en cualquier átomo disponible para producir un compuesto estable. Preferiblemente, la sustitución de alcoxi inferior es con 1, 2, 3, 4, o 5 sustituyentes, también 1, 2, o 3 sustituyentes. Por ejemplo "alcoxi inferior sustituido con flúor" denota alcoxi inferior en el cual el alquilo inferior se sustituye con uno o más átomos de flúor, donde preferiblemente el alcoxi inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Aunque se entiende que las sustituciones en alcoxi se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución de alcoxi es tal que -O-, -S-, o –N- (excepto donde N es un átomo de anillo heteroarilo), no se unen al carbono del alquilo unido al alcoxi -O-. Además, donde alcoxi se describe como sustituyente de otra porción, el oxígeno de alcoxi no se une a un átomo de carbono que se une a un –O-, -S-, o –N- de la otra porción (excepto donde N es un átomo de anillo heteroarilo), o a un carbono de alqueno o alquino de la otra porción.

[0072] "Alquiltio inferior" denota el grupo $-SR^{aa}$, donde R^{aa} es alquilo inferior. "Alquiltio inferior sustituido" denota alquiltio inferior en el cual R^{aa} es alquilo inferior sustituido con uno o más sustituyentes, como se indica en este documento, unidos en cualquier átomo disponible para producir un compuesto estable. Preferiblemente, la sustitución de alquiltio inferior es con 1, 2, 3, 4, o 5 sustituyentes, también 1, 2, o 3 sustituyentes. Por ejemplo "alquiltio inferior sustituido con flúor" denota alquiltio inferior en el cual el alquilo inferior se sustituye con uno o más átomos de flúor, donde preferiblemente el alquiltio inferior se sustituye con 1, 2, 3, 4 o 5 átomos de flúor, también 1, 2, o 3 átomos de flúor. Aunque se entiende que las sustituciones en alquiltio se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución de alquiltio es tal que -O-, -S-, o –N- (excepto donde N es un átomo de anillo heteroarilo), no se unen al carbono del alquilo unido al alquiltio -S-. Además, donde el alquiltio se describe como sustituyente de otra porción, el azufre del alquiltio no se une a un átomo de carbono que se une a un –O-, -S-, o –N- de la otra porción (excepto donde N es un átomo de anillo heteroarilo), o a un carbono de alqueno o alquino de la otra porción.

[0073] "Mono-alquilamino" denota el grupo $-NHR^{bb}$ donde R^{bb} es alquilo inferior. "Di-alquilamino" denota el grupo $-NR^{bb}R^{cc}$, donde R^{bb} y R^{cc} son independientemente alquilo inferior. "Cicloalquilamino" denota el grupo $-NR^{dd}R^{ee}$, donde R^{dd} y R^{ee} 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. Aunque se entiende que cuando mono-alquilamino, di-alquilamino, o cicloalquilamino son sustituyentes en otras porciones que se unen en cualquier átomo disponible para producir un compuesto estable, el nitrógeno de mono-alquilamino, di-alquilamino, o cicloalquilamino como sustituyentes no se une a un átomo de carbono que se une a un –O-, -S-, o –N- de la otra porción.

[0074] Como se usa en este documento, el término enfermedad o padecimiento mediado por c-kit se refiere a una enfermedad o padecimiento en el cual la función biológica de c-kit afecta el desarrollo y/o curso de la enfermedad o padecimiento, y/o en el cual la modulación de c-kit altera el

desarrollo, curso, y/o síntomas. Por ejemplo, mutaciones en el gen c-kit tales como las mutaciones W42, Wv, y W41 reportadas por Herbst et al al (J. Biol. Chem., 1992, 267: 13210-13216) confieren características fenotípicas severas, intermedias, y moderadas, respectivamente. Estas mutaciones atenúan la actividad intrínseca de tirosina cinasa del receptor a diferentes grados y son modelos para el efecto de modulación de actividad de c-kit. Una enfermedad o padecimiento mediado por c-kit incluye una enfermedad o padecimiento para el cual la inhibición de c-kit proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con inhibidores de c-kit, incluyendo compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0075] Como se usa en este documento, el término enfermedad o padecimiento mediado por c-fms se refiere a una enfermedad o padecimiento en el cual la función biológica de c-fms afecta el desarrollo y/o curso de la enfermedad o padecimiento, y/o en el cual la modulación de c-fms altera el desarrollo, curso, y/o síntomas. Por ejemplo, el ratón mutante *Csf1r⁻/Csf1r⁻* de Dai et al (Blood, 2002, **99**: 111-120) que carece de c-fms es un modelo animal para enfermedades o padecimientos en donde la actividad de c-fms se ha eliminado. Una enfermedad o padecimiento mediado por c-fms incluye una enfermedad o padecimiento para el cual la inhibición de c-fms proporciona un beneficio terapéutico, por ejemplo, en donde el tratamiento con inhibidores de c-fms, incluyendo compuestos descritos en este documento, proporciona un beneficio terapéutico al sujeto que adolece o está en riesgo de la enfermedad o padecimiento.

[0076] Como se usa en este documento, el término "composición" se refiere a una formulación adecuada para su administración a un sujeto animal pretendido para propósitos terapéuticos, que contiene al menos un compuesto farmacéuticamente activo y al menos un portador o excipiente farmacéuticamente aceptable.

[0077] 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.

[0078] En el presente contexto, los términos "terapéuticamente efectiva" y "cantidad efectiva" indican que los materiales o cantidad de material son efectivos 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.

[0079] 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 c-kit o c-fms. Por ejemplo, una agonista o antagonista de una biomolécula particular modula la actividad de esa biomolécula, *por ejemplo*, una enzima.

[0080] El término "actividad de c-kit" se refiere a una actividad biológica de c-kit, que particularmente incluye actividad de cinasa. El término "actividad de c-fms" se refiere a una actividad biológica de c-fms, que particularmente incluye actividad de cinasa.

I. General

[0081] En un aspecto, la presente invención concierne a compuestos de la Fórmula II, IIa, IIb, IIe, IIg, IIp o III y todas las sub-modalidades de los mismos, que son inhibidores de c-kit, c-fms, o tanto de c-kit como de c-fms, y el uso de los compuestos para tratar enfermedades que se median por c-kit, c-fms, o tanto c-kit como c-fms.

Enfermedades Ejemplares Asociadas con c-Kit.

[0082] Los compuestos descritos en este documento son útiles para tratar trastornos relacionados con c-kit, por ejemplo, enfermedades relacionadas con transducción de señales por cinasas no reguladas, incluyendo trastornos proliferativos celulares, trastornos fibróticos y trastornos metabólicos, entre otros. Como se describe en mayor detalle posteriormente y en Lipson et al., U.S. 20040002534 (Solicitud Estadounidense 10/600, 868, presentada el 23 de junio de 2003) que se incorpora en este documento como referencia en su totalidad, los trastornos proliferativos celulares que pueden tratarse por la presente invención incluyen cánceres, y trastornos proliferativos de mastocitos.

[0083] La presencia de c-kit también se ha asociado con una serie de tipos diferentes de cánceres. Además, la asociación entre anormalidades en c-kit y la enfermedad no se restringe a cáncer. Como tal, c-kit se ha asociado con malignidades, incluyendo tumores de mastocitos, cáncer de

pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal (GISTs), glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mielocítica aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mastocitosis, melanoma, y tumores de mastocitos caninos, y enfermedades inflamatorias, incluyendo asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, e hipereosinofilia.

Enfermedades Ejemplares Asociadas con c-fms

[0084] La presencia de c-fms se ha asociado con una serie de tipos diferentes de enfermedades. Como tal, c-fms se ha asociado con trastornos inmunes, incluyendo artritis reumatoide, lupus eritematoso sistémico (SLE), y rechazo de transplantes; enfermedades inflamatorias incluyendo síndrome inflamatorio intestinal, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica (COPD), enfisema, y ateroesclerosis; trastornos metabólicos, incluyendo Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, y lipólisis; trastornos de estructura ósea, mineralización y formación y resorción ósea, incluyendo osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia, y metástasis de cáncer a hueso; enfermedades renales, incluyendo nefritis (por ejemplo, glomerulonefritis, nefritis intersticial, nefritis por Lupus), necrosis tubular, complicaciones renales asociadas a diabetes (por ejemplo, nefropatía diabética), e hipertrofia; trastornos del sistema nervioso central, incluyendo esclerosis múltiple, apoplejía, enfermedad de Alzheimer y enfermedad de Parkinson, dolor inflamatorio y crónico, incluyendo dolor óseo; y cánceres, incluyendo mieloma múltiple, leucemia mieloide aguda, leucemia mieloide crónica (CML), cáncer de próstata, cáncer de mama, cáncer ovárico, y metástasis de tumores a otros tejidos.

Enfermedades Ejemplares Asociadas con TrkA y TrkB

[0085] **TrkA:** Cinasa objetivo TrkA (es decir, tirosina cinasa neurotrófica, receptor, tipo 1) es una tirosina cinasa de 87.5 kDa codificada por el cromosoma 1q21-q22 (símbolo: NTRK1). Los inhibidores de TrkA pueden ser útiles para tratar dolor (por ejemplo, dolor crónico, dolor neuropático), cáncer (por ejemplo, cáncer de próstata, cáncer de pulmón, cáncer pancreático),

artritis, retinopatía diabética, degeneración macular y psoriasis.

[0086] **TrkB:** Cinasa objetivo TrkB (es decir, tirosina cinasa neurotrófica, receptor, tipo 2) es una tirosina cinasa de 92 kDa codificada por el cromosoma 9q22.1 (símbolo: NTRK2). Los inhibidores de TrkB pueden ser útiles para tratar cáncer (por ejemplo, cáncer de próstata, cáncer de pulmón, tumores de Wilms, neuroblastoma, cáncer pancreático).

Enfermedades Ejemplares Asociadas con HGK

[0087] **HGK:** Cinasa objetivo HGK (es decir, proteína cinasa cinasa cinasa cinasa 4 activada por motógenos) es una serina/treonina cinasa de 130 kDa codificada por el cromosoma 2q11.2-q12 (símbolo: MAP4K4). Los inhibidores de HGK pueden ser útiles para tratar indicaciones metabólicas, incluyendo re-sensibilizar células grasas y musculares a insulina, mejorar la patología en adipocitos, mejorar la patología en células musculares, y diabetes tipo II; una amplia variedad de indicaciones oncológicas, incluyendo bloquear la migración, invasión y metástasis en muchos tipos diferentes de tumores; y enfermedades autoinmunes mediadas por células T.

IV. Ensayos de Actividad Cinasa

[0088] Una serie de diferentes ensayos para actividad de cinasa puede utilizarse para probar moduladores activos y/o determinar la especificidad de un modulador para una cinasa particular o grupo o cinasas. Además del ensayo mencionado en los ejemplos posteriormente, un experto en la técnica sabrá de otros ensayos que pueden utilizarse y puede modificar un ensayo para una aplicación particular. Por ejemplo, numerosos artículos concernientes a ensayos descritos de cinasas que pueden usarse.

[0089] Ensayos alternativos adicionales pueden emplear determinaciones de unión. Por ejemplo, esta clase de ensayo puede configurarse ya sea en un formato de transferencia de energía por resonancia de fluorescencia (FRET), o usando un formato de AlfaScreen (*e*nsayo *h*omogéneo de *p*roximidad *l*uminescente *a*mplificada) al variar los reactivos donador y aceptor que se unen a estreptavidina o al anticuerpo fosfo-específico.

V. Técnicas Sintéticas Orgánicas

[0090] Una amplia variedad de técnicas sintéticas orgánicas existen en el arte para enfrentar el reto de construir moduladores potenciales. Muchos de estos métodos sintéticos orgánicos se

describen en detalle en fuentes estándar de referencia utilizadas por los expertos en la técnica. Un ejemplo de tal referencia es marzo, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, Nueva 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.

VI. Formas o Derivados de Compuestos Alternativos

[0091] Formas o derivados alternativos, tales como (a) Isómeros, Profármacos, y Metabolitos activos (b) Tautómeros, Estereoisómeros, Regioisómeros, y Formas Solvatadas (c) Profármacos y Metabolitos (d) Sales farmacéuticamente aceptables y (e) Formas polimórficas, se describen, por ejemplo, en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519, cuya descripción se incorpora por la presente como referencia en su totalidad.

VII. Administración

[0092] 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. En esto contexto, los términos "sujeto", "sujeto animal", y similares se refieren a vertebrados humanos y no humanos, por ejemplo, mamíferos, tales como primates no humanos, animales para deportes y comerciales, por ejemplo, equinos, bovinos, porcinos, ovinos, roedores, y mascotas, por ejemplo, caninos y felinos. Una descripción de posibles métodos y rutas de administración puede encontrarse, por ejemplo, en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519, cuya descripción se incorpora por la presente como referencia en su totalidad.

EJEMPLOS

[0093] Una serie de ejemplos ilustrativos de la presente invención se describe a continuación. En la mayoría de los casos, técnicas alternativas también pueden usarse. Los ejemplos pretenden ser ilustrativos y no son limitantes o restrictivos para el alcance de la invención. A menos que se advierta específicamente lo contrario, en los casos donde un número de compuesto no se precede por una "P-" (por ejemplo, "P-0001") en la sección de ejemplos, el nombre y/o enumeración del compuesto no se relaciona con el nombre y/o enumeración empleada en otras secciones de esta

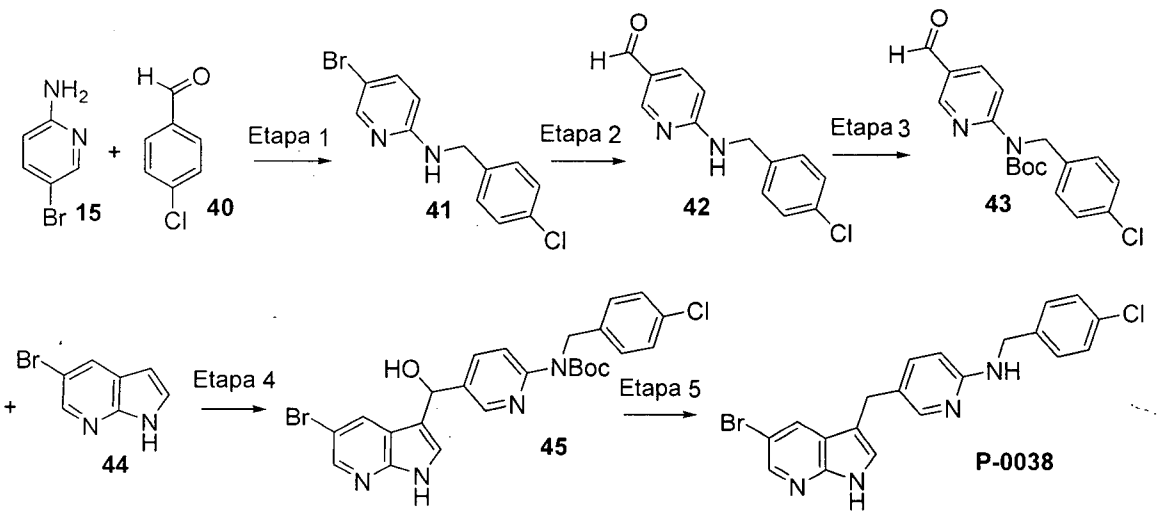
solicitud. De manera similar, el nombre y enumeración de estructuras y sustituyentes dentro de los ejemplos son independientes del nombre y enumeración de estructuras y sustituyentes en secciones anteriores de esta solicitud, a menos que se indique claramente de otra manera.

[0094] En los siguientes Ejemplos, se entiende que los solventes y reactivos usados o sugeridos no son limitantes, y pueden sustituirse apropiadamente con solventes y reactivos conocidos por los expertos en la técnica. Los productos de reacción pueden aislarse por medios conocidos en la técnica, tal como extracción con un solvente adecuado, precipitación a partir de un solvente adecuado, cromatografía usando un sistema de solventes adecuado, incluyendo cromatografía de columna en gel de sílice, HPLC, TLC preparativa, y similares. Métodos ejemplares para la síntesis de los compuestos de la presente invención pueden encontrarse en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519, cuya descripción se incorpora por la presente como referencia. El núcleo 1H-pirrolo[2,3-b]piridina de los compuestos descritos en los ejemplos también puede referirse como 7-azaindol en los ejemplos.

Ejemplo 1: Síntesis de [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-cloro-bencil)-amina (P-0038)

[0095] [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-cloro-bencil)-amina **P-0038** se sintetizó en 5 etapas a partir de 2-Amino-5-bromopiridina **15** comercialmente disponible, como se muestra en el Esquema 19.

Esquema 19



Etapa 1- Síntesis de (5-Bromo-piridin-2-il)-(4-cloro-bencil)-amina **(41)**

[0096] A 2-Amino-5-bromopiridina (**15**, 6.10 g, 0.0352 mol) en tolueno (90.0 ml) se agregaron 4-clorobenzaldehído (**40**, 5.00 g, 0.0356 mol), ácido trifluoroacético (8.0 ml, 0.10 mol) y trietilsilano (16.5 ml, 0.103 mol). La reacción se calentó a reflujo durante 48 horas. La reacción se concentró, se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se concentró. El residuo sin purificar se cristalizó con acetato de etilo para dar el compuesto (**41**, 6.8 g, 65.4%).

Etapa 2 – Síntesis de 6-(4-Cloro-bencilamino)-piridina-3-carbaldehído **(42)**

[0097] A (5-Bromo-piridin-2-il)-(4-cloro-bencil)-amina (**41**, 10.00 g, 0.03360 mol) en tetrahidrofurano (400.0 ml) bajo una atmósfera de nitrógeno a -78 °C se agregó n-butilitio (17.5 ml, 2.00 M en ciclohexano). Después de 90 minutos, ter-butilitio (42.00 ml, 1.70 M en hexano) se agregó a la reacción. Después de 80 minutos, N,N-dimetilformamida (6.9 ml, 0.089 mol) se agregó a la reacción. La mezcla de reacción se agitó a -78 °C durante 2 horas, luego se dejó entibiar a temperatura ambiente durante 1 hora. 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 y se concentró para dar el compuesto sin purificar, que se cristalizó a partir de metiléter de *ter*-butoxilo para proporcionar el compuesto (**42**, 7.66 g, 92.2%).

Etapa 3 – Síntesis de ter-butiléster del ácido (4-Cloro-bencil)-(5-formil-piridin-2-il)-carbámico **(43)**

[0098] A 6-(4-Cloro-bencilamino)-piridina-3-carbaldehído (**42**, 2.00 g, 8.11 mmol) en diclorometano (20.0 ml) se agregaron trietilamina (1.70 ml, 12.2 mmol), di-ter-butildicarbonato (2.00 g, 9.16 mmol) y 4-dimetilaminopiridina (52.3 mg, 0.43 mmol). La reacción se agitó a temperatura ambiente durante 48 horas. La reacción se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano para dar el compuesto (**43**, 2.50 g, 89.3%).

Etapa 4 – Síntesis de ter-butiléster del ácido {5-[(5-Bromo-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il}-(4-cloro-bencil)-carbámico **(45)**

[0099] A 5-bromo-7-azaindol (**44**, 198.0 mg, 1.01 mmol) en metanol (30.0 ml, 0.741 mol) se agregaron ter-butiléster del ácido (4-Cloro-bencil)-(5-formil-piridin-2-il)-carbámico (**43**, 355.0 mg, 1.02 mmol) e hidróxido de potasio (80.0 mg, 1.42 mmol). La reacción se agitó a temperatura

ambiente 48 horas. 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 concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 8% de metanol en diclorometano para dar el compuesto (**45**, 200.0 mg, 36.8%).

Etapa 5 – Síntesis de [5-(5-Bromo-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-cloro-bencil)-amina **(P-0038)**

[0100] A ter-butiléster del ácido {5-[(5-Bromo-1H-pirrolo [2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il}-(4-cloro-bencil)-carbámico (**45**, 180.0 mg, 0.33 mmol) en acetonitrilo (30.0 ml) se agregaron ácido trifluoroacético (2.0 ml, 0.026 mol) y trietilsilano (4.0 ml, 0.025 mol). La reacción se calentó a reflujo durante 4 horas. 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 concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 10% de metanol en diclorometano para dar el compuesto (**P-0038**, 120 mg, 85.2%). MS(ESI)$[M+H^+]^+$ = 427.2, 429.2.

[0101] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 19, reemplazando opcionalmente 4-clorobenzaldehído **40** con un aldehído apropiado en la Etapa 1 y reemplazando opcionalmente 5-bromo-7-azaindol **44** con un azaindol apropiado en la Etapa 4. Los siguientes compuestos se produjeron siguiendo este procedimiento:

[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**),

3-[6-(4-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0257**),

3-[6-(4-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0269**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-bencil)-amina (**P-0270**),

3-[6-(2-fluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0271**),

(2-fluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0272**),

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0273**),

3-[6-(2-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0274**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina (**P-0275**),

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina (**P-0276**),

3-[6-(2,6-Difluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0277**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-difluoro-bencil)-amina (**P-0278**),

(2-Cloro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0279**),

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0280**),

3-[6-(2-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0281**),

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0282**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-0283**),

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-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]piridina-5-carbonitrilo (**P-0287**),

(2-Etoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0288**),

(2,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0296**),

(2,5-Difluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0297**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,5-difluoro-bencil)-amina (**P-0298**),

3-[6-(2,5-Difluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0299**),

3-[6-(2-Trifluorometoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0321**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometoxi-bencil)-amina (**P-0322**),

3-[6-(2-Etoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0323**),

[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina (**P-0325**),

[5-(5-Metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina (**P-0326**),

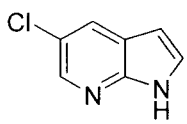
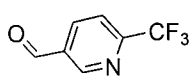
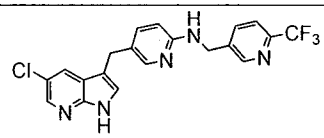
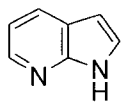
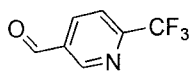
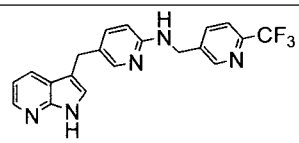
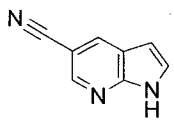
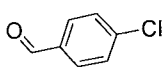
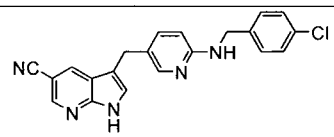
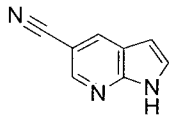
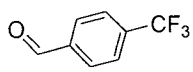
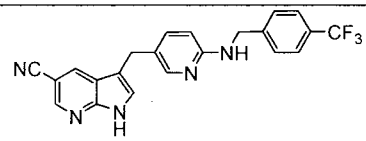
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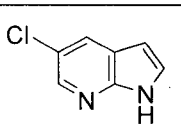
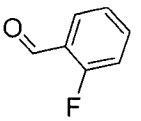
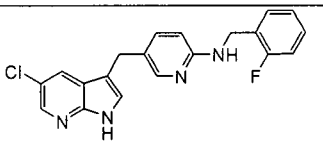
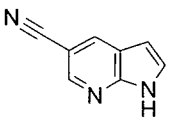
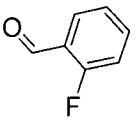
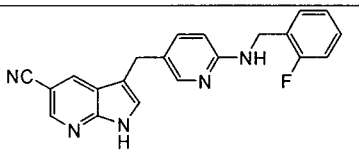
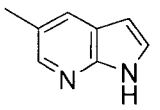
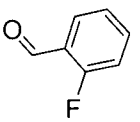
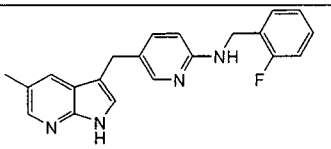
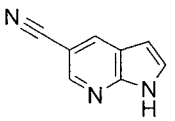
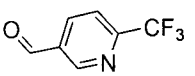
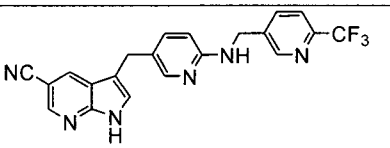
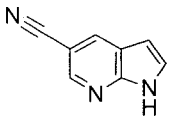
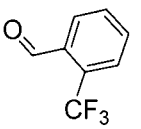
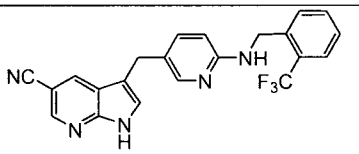
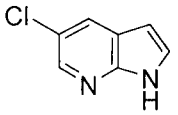
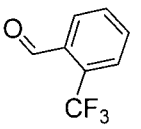
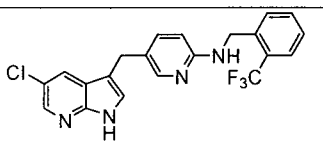
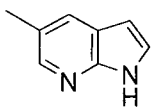
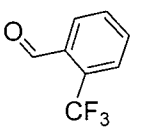
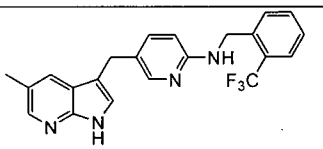
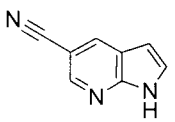
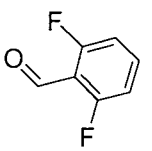
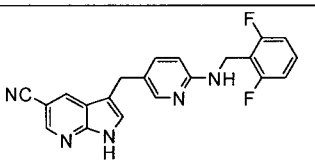
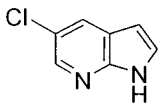
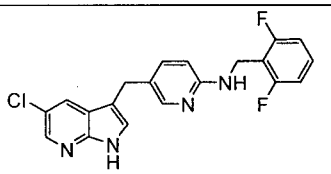
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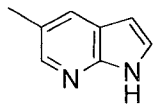
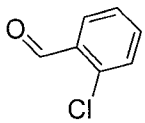
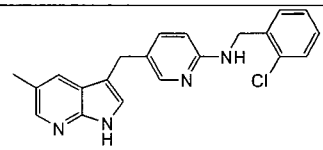
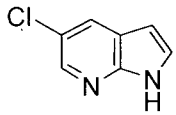
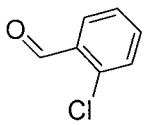
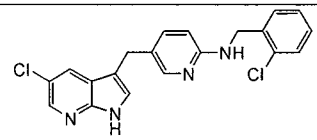
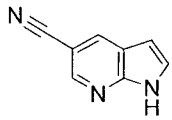
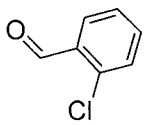
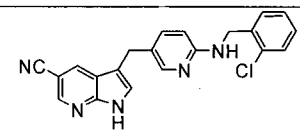
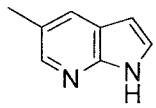
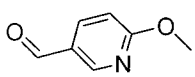
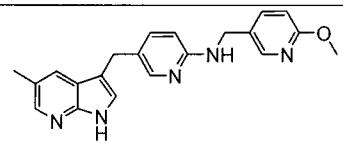
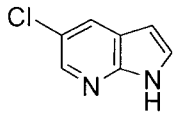
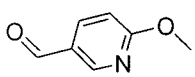
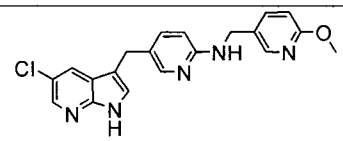
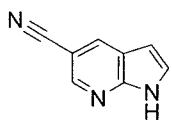
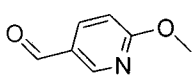
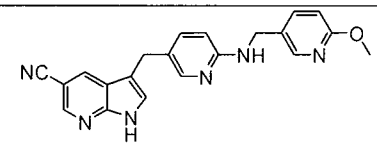
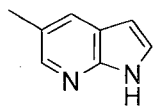
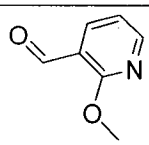
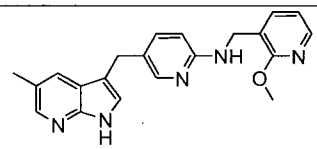
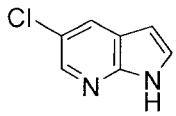
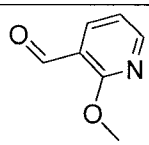
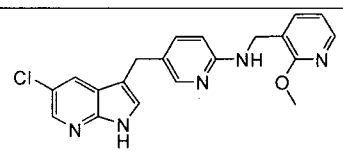
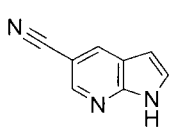
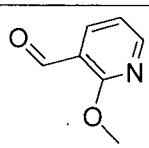
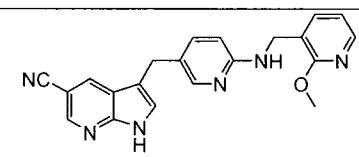
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(2,5-Difluoro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0329**), (2,5-Difluoro-bencil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0330**), [5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-0331**), (6-Metoxi-piridin-3-ilmetil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0332**), (2,6-Difluoro-bencil)-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0333**), (2,6-Difluoro-bencil)-[5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0334**), (2-Metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0336**), 3-[6-(2-Metoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0337**), (2,6-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0340**), y (2,6-Difluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0341**).

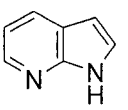
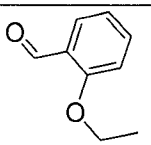
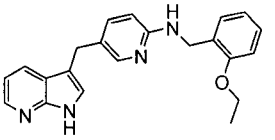
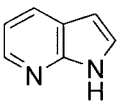
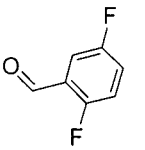
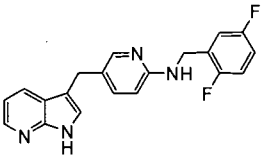
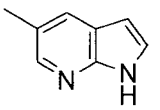
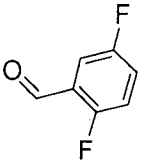
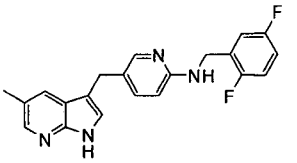
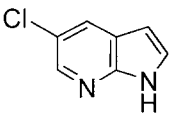
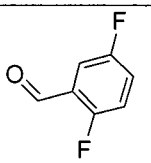
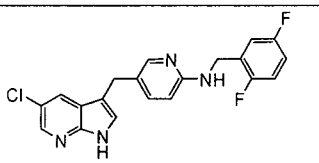
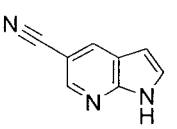
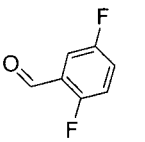
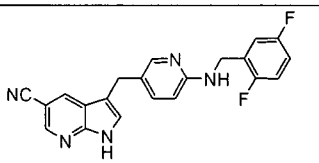
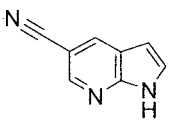
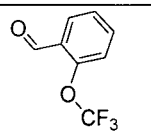
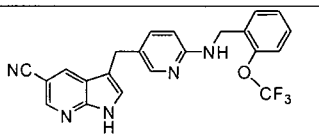
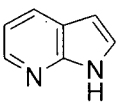
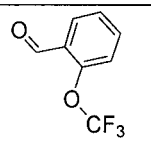
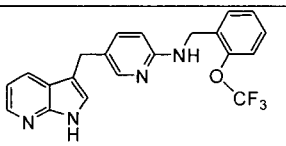
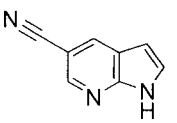
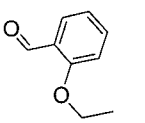
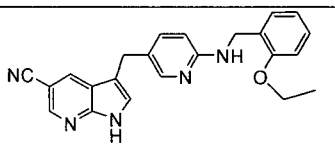
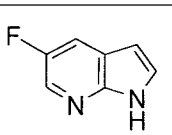
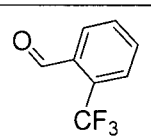
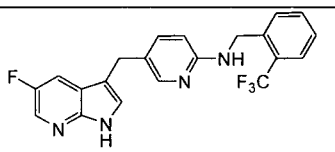
La siguiente tabla indica el aldehído usado en la Etapa 1 en la Columna 3 y el azaindol usado en la Etapa 4 en la Columna 2 para proporcionar el compuesto de la Columna 4. La Columna 1 proporciona el número de compuesto y la Columna 5 el resultado medido de la espectrometría de masas.

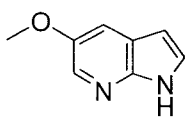
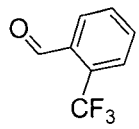
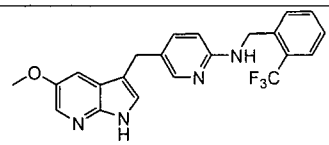
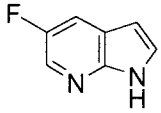
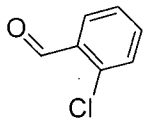
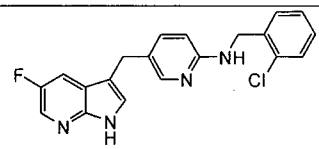
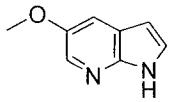
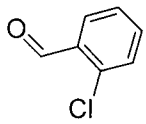
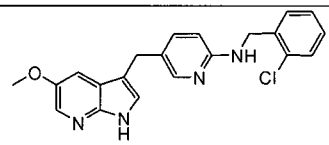
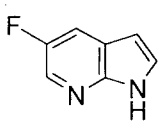
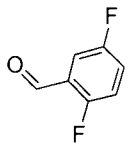
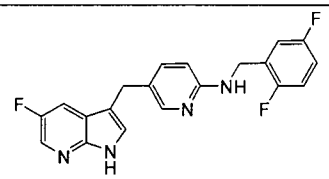
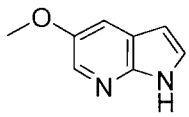
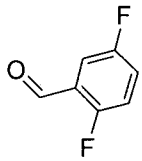
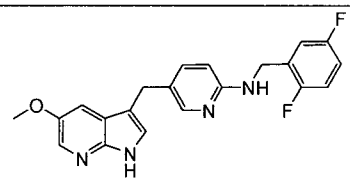
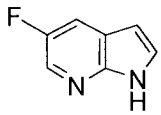
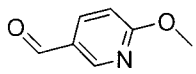
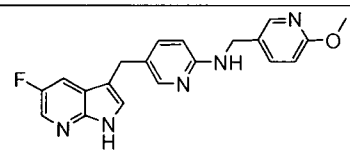
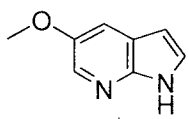
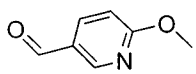
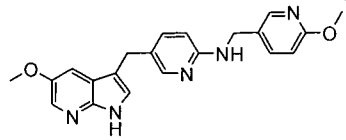
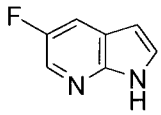
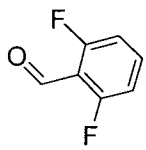
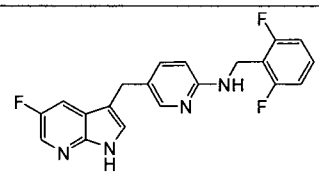
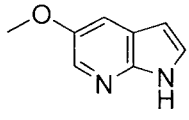
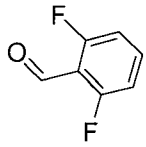
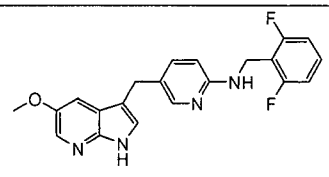
Número de compuesto	Azaindol en Etapa 4	Aldehído en Etapa 1	Estructura del compuesto	MS $[M+H^+]^+$
P-0181				418.2
P-0182				384.2
P-0257				374.2
P-0269				408.7

P-0270				367.0
P-0271				358.0
P-0272				347.0
P-0273				409.4
P-0274				408.5
P-0275				417.0
P-0276				397.6
P-0277				376.5
P-0278				385.0

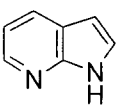
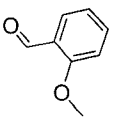
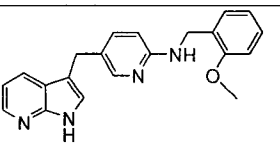
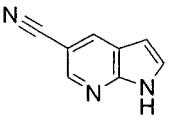
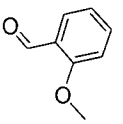
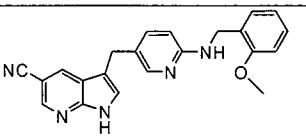
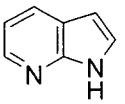
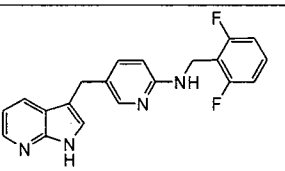
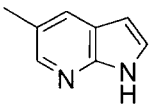
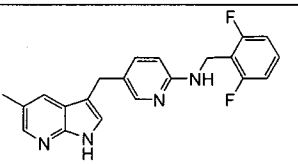
P-0279				363.0
P-0280				383.3
P-0281				374.0
P-0282				360.8
P-0283				380.0
P-0284				371.5
P-0285				360.1
P-0286				380.0
P-0287				371.0

274

P-0288				359.6
P-0296				351.6
P-0297				365.5
P-0298				385.9
P-0299				376.4
P-0321				424.6
P-0322				399.5
P-0323				384.7
P-0325				401.5

P-0326				413.4
P-0327				367.2
P-0328				379.0
P-0329				369.7
P-0330				381.6
P-0331				364.5
P-0332				376.4
P-0333				369.6
P-0334				381.6

276

P-0336				345.7
P-0337				370.7
P-0340				351.5
P-0341				365.5

[0102] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 19, Etapas 4 y 5, reemplazando ter-butiléster del ácido (4-Cloro-bencil)-(5-formil-piridin-2-il)-carbámico **43** con un aldehído protegido apropiado y 5-bromo-7-azaindol **44** con un azaindol apropiado en la Etapa 4. Los aldehídos se prepararon como se describe en el Ejemplo 60. Los siguientes compuestos se produjeron siguiendo este procedimiento:

3-{2-Cloro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-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**),

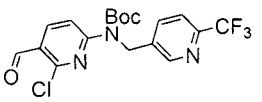
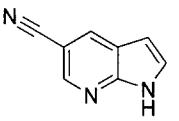
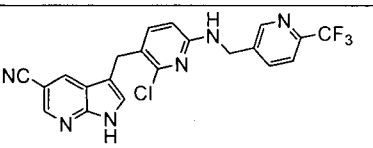
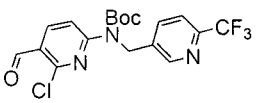
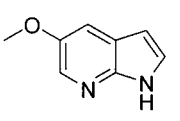
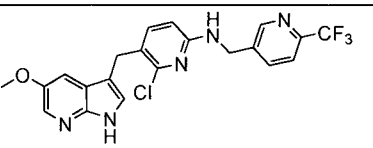
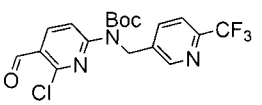
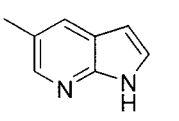
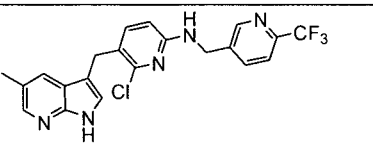
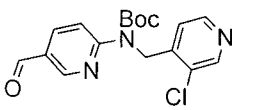
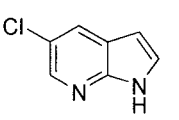
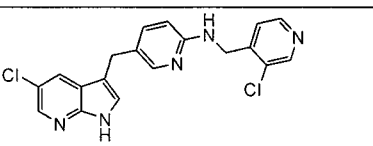
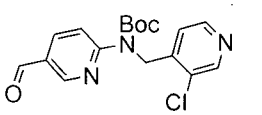
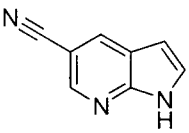
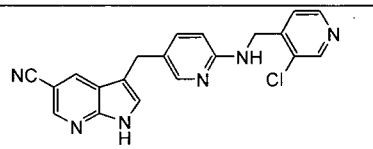
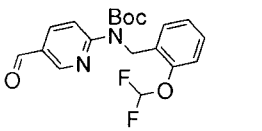
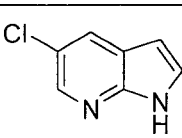
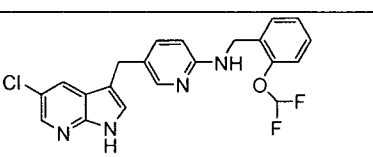
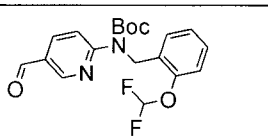
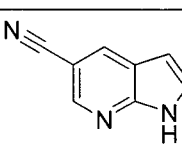
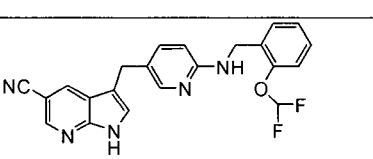
(3-Cloro-piridin-4-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0235**),

3-{6-[(3-Cloro-piridin-4-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0256**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-difluorometoxi-bencil)-amina (**P-0338**),

3-[6-(2-Difluorometoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo (**P-0339**),

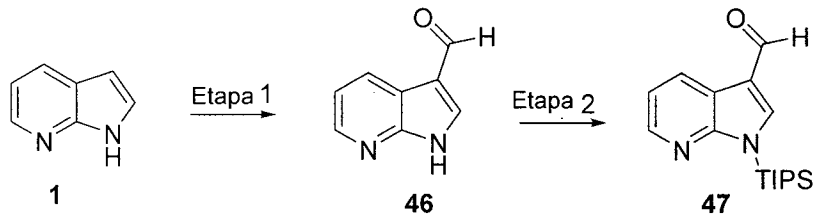
La siguiente tabla indica el aldehído usado en la Columna 2 y el azaindol usado en la Columna 3 para proporcionar el compuesto de la Columna 4. La Columna 1 proporciona el número de compuesto y la Columna 5 el resultado medido de la espectrometría de masas.

Número de compuesto	Aldehído	Azaindol	Compuesto	MS $[M+H^+]^+$
P-0232				443.0
P-0233				$[M-H^+]^-$ = 446.1
P-0234				430.1
P-0235				383.9
P-0256				375.2
P-0338				415.0
P-0339				406.6

Ejemplo 2: Síntesis de 1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-carbaldehído 47.

[0103] El compuesto **47** se sintetizó en 2 etapas a partir de 7-azaindol **1** como se describe en el Esquema 20.

Esquema 20



1 **46** **47**

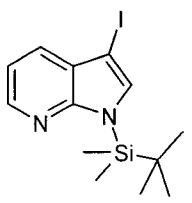
Etapa 1 – *Preparación de 1H-pirrolo[2,3-b]piridina-3-carbaldehído* **(46)**:

[0104] A 1H-Pirrolo[2,3-b]piridina (**1**, 16.0 g, 135 mmol) en agua (110 ml), se agregaron hexametilenotetramina (26.0 g, 185 mmol), y ácido acético (55.0 ml, 967 mmol). La reacción se sometió a reflujo durante 12 horas. Agua (329 ml) se agregó y la reacción se enfrió a temperatura ambiente. La reacción se filtró y lavó con agua para dar el compuesto (**46**, 15.0 g, 76%). MS(ESI)$[M+H^+]^+$ = 147.

Etapa 2 – *Preparación de 1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-carbaldehído* **(47)**:

[0105] A 1H-Pirrolo[2,3-b]piridina-3-carbaldehído (**46**, 4.05 g, 27.71 mmol) en tetrahidrofurano (30.0 ml) se agregaron hidruro de sodio (60% en aceite mineral, 1.5 g, 38 mmol) y cloruro de triisopropilsililo (8.0 ml, 38 mmol) bajo una atmósfera de nitrógeno. La reacción se agitó durante 2 horas a temperatura ambiente. 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 10 % de acetato de etilo en hexano para dar el compuesto (**47**, 3.0 g, 36%). MS(ESI)$[M+H^+]^+$ = 303.

[0106] 1-(ter-Butil-dimetil-silanil)-3-yodo-1H-pirrolo[2,3-b]piridina **66**

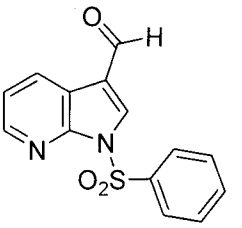


se preparó siguiendo el protocolo del Esquema 20 Etapa 2, sustituyendo 1H-Pirrolo[2,3-b]piridina-3-carbaldehído **46** con 3-yodo-1H-pirrolo[2,3-b]piridina y cloruro de triisopropilsililo con cloruro de

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ter-Butil-dimetil-sililo.

[0107] 1-Bencensulfonil-1H-pirrolo[2,3-b]piridina-3-carbaldehído **55**

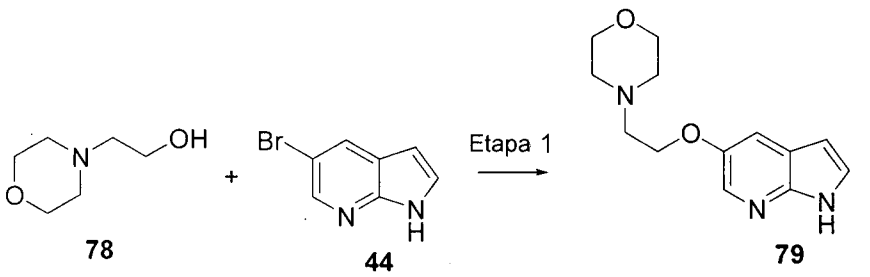


se preparó siguiendo el protocolo del Esquema 20, sustituyendo cloruro de triisopropilsililo con cloruro de bencensulfonilo en la Etapa 2.

Ejemplo 3: Síntesis de intermediarios de 7-azaindol 5 sustituidos

[0108] 5-(2-Morfolin-4-il-etoxi)-1H-pirrolo[2,3-b]piridina **79** se sintetizó en 1 Etapa a partir de 5-bromo-azaindol comercialmente disponible como se muestra en el Esquema 31.

Esquema 31



Etapa 1 – 5-(2-Morfolin-4-il-etoxi)-1H-pirrolo[2,3-b]piridina **(79)**:

[0109] A 4-morfolinetanol (30 ml, 0.2 mol) en N, N-dimetilformamida (30 ml) se agregó lentamente hidruro de sodio (7 g, dispersión al 60% en aceite mineral, 0.2 mol). Después de que la solución se volvió transparente, una solución de 5-bromo-7-azaindol (**44**, 1.0 g, 0.0051 mol) en N,N-dimetilformamida (5 ml) y bromuro de cobre(I) (1.4 g, 0.0098 mol) se agregaron. La mezcla de reacción se agitó a 120 °C bajo nitrógeno durante 2 horas. La mezcla de reacción se concentró y el residuo se disolvió en acetato de etilo y agua. La capa orgánica se recolectó, se lavó con una solución de cloruro de amonio e hidróxido de amonio (4:1), salmuera, y se secó sobre sulfato de magnesio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo en hexano para proporcionar el compuesto

280

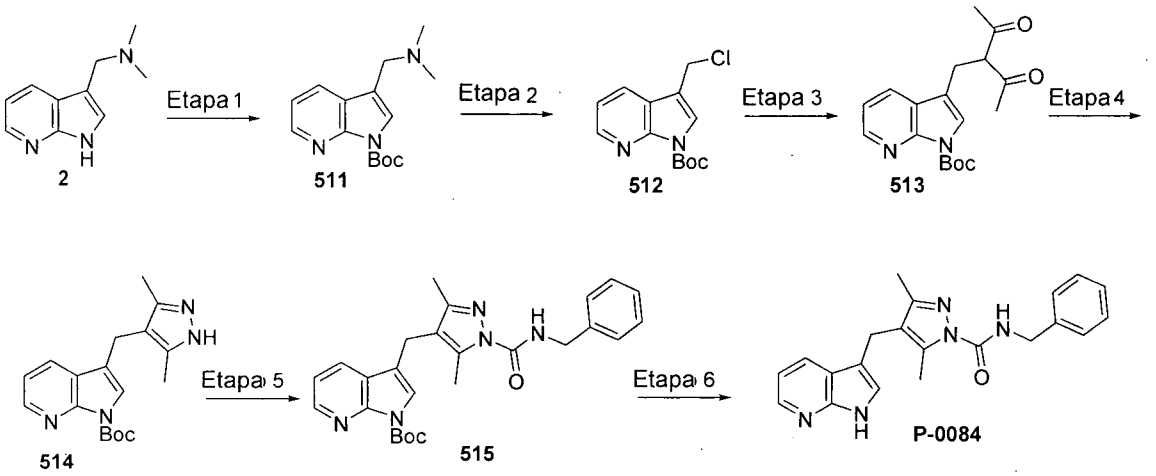
como un sólido blanquecino (**79**, 0.62 g, 50%). MS (ESI) $[M+H^+]^+$ = 248.25.

[0110] 7-azaindoles 5-sustituidos adicionales se prepararon siguiendo el protocolo del Esquema 31, reemplazando 4-morfolinetanol ya sea con 2-dietilamino-etanol, 3-dietilamino-propan-1-ol, 2-piperidin-1-il-etanol, o 2-pirrolidin-1-il-etanol para proporcionar dietil-[2-(1H-pirrolo[2,3-b]piridin-5-iloxi)-etil]-amina, Dietil-[3-(1H-pirrolo[2,3-b]piridin-5-iloxi)-propil]-amina, 5-(2-piperidin-1-il-etoxi)-1H-pirrolo[2,3-b]piridina, y 5-(2-pirrolidin-1-il-etoxi)-1H-pirrolo[2,3-b]piridina, respectivamente.

Ejemplo 4: Síntesis de bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico P-0084

[0111] La bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico P-0084 se sintetizó en 6 etapas a partir de dimetil-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-amina **2** como se muestra en el Esquema 158.

Esquema – 158



*Etapa 1: Preparación de ter-butiléster del ácido 3-Dimetilaminometil-pirrolo[2,3-b]piridina-1-carboxílico (**511**)*

[0112] A dimetil-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-amina (**2**, 2.50 g, 14.3 mmol,) en tetrahidrofurano (200.0 ml) se agregó hidruro de sodio (0.685 g, 60% en aceite mineral, 17.1 mmol). Después de 10 minutos, di-*ter*-butildicarbonato (3.74 g, 17.1 mmol) se agregó a la reacción. La reacción se agitó a temperatura ambiente durante la noche. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 30% de acetato de etilo en

hexano para darse como un sólido blanco (**511**, 3.80 g, 96.7%).

*Etapa 2: Preparación de ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**512**)*

[0113] A ter-butiléster del ácido 3-Dimetilaminometil-pirrolo[2,3-b]piridina-1-carboxílico (**511**, 2.60 g, 9.44 mmol) en tolueno (50.00 ml) se agregó cloroformato de isopropilo (11.3 ml, 1.0 M en tolueno) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante 3 horas. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano para dar un sólido blanco (**512**, 2.0 g, 79.4%).

*Etapa 3 – Preparación de ter-butiléster del ácido 3-(2-Acetil-3-oxo-butil)-pirrolo[2,3-b]piridina-1-carboxílico (**513**):*

[0114] A acetilacetona (0.563 g, 5.62 mmol) en sulfóxido de dimetilo (29.0 ml) se agregó hidruro de sodio (0.225 g, 60% en aceite mineral, 5.62 mmol). Después de 20 minutos, ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**512**, 1.00 g, 3.75 mmol) se agregó a la reacción. La reacción se agitó a temperatura ambiente durante 2 horas. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 40% de acetato de etilo en hexano para dar un aceite incoloro (**513**, 0.59 g, 48.0%). MS (ESI) $[M+H^+]^+$ = 331.4.

*Etapa 4 – Preparación de ter-butiléster del ácido 3-(3,5-Dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**514**)*

[0115] A ter-butiléster del ácido 3-(2-Acetil-3-oxo-butil)-pirrolo[2,3-b]piridina-1-carboxílico (**513**, 1.20 g, 3.63 mmol) en metanol (15.0 ml), enfriado a -20 °C bajo una atmósfera de nitrógeno, se agregó hidrazina (0.128 g, 4.00 mmol) en diclorometano (6.0 ml). La reacción se agitó durante 2 horas. La reacción se concentró para remover los solventes, y el residuo 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 60% de acetato de

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etilo en hexano para dar un sólido blanco (**514**, 1.0 g, 84.4%). MS (ESI) $[M+H^+]^+$ = 327.4.

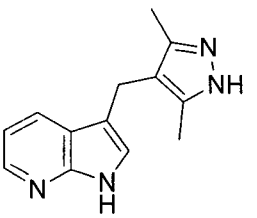
*Etapa 5 – Preparación de ter-butiléster del ácido 3-(1-Bencilcarbamoil-3,5-dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**515**)*

[0116] A ter-butiléster del ácido 3-(3,5-Dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**514**, 60.0 mg, 0.18 mmol) en diclorometano (6.0 ml) se agregaron 1,8-diazabiciclo[5.4.0]undec-7-eno (0.033 ml, 0.220 mmol) e isocianato de bencilo (29.4 mg, 0.220 mmol) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante 2 horas. La reacción se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 30% de acetato de etilo en hexano para dar el compuesto sin purificar (**515**, aprox. 50 mg) que se usó en la siguiente etapa directamente. MS (ESI) $[M+H^+]^+$ = 460.5.

*Etapa 6 - bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0084**)*

[0117] A ter-butiléster del ácido 3-(1-Bencilcarbamoil-3,5-dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**515**, 50.0 mg, 0.11 mmol) en diclorometano (6.0 ml) se agregó ácido trifluoroacético (0.20 ml, 2.6 mmol) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante 20 minutos. 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 30% de acetato de etilo en hexano para dar un sólido blanco (**P-0084**, 11.0 mg, 28.1%). MS (ESI) $[M+H^+]^+$ = 360.5.

[0118] 3-(3,5-Dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina **P-0124**



se preparó a partir de ter-butiléster del ácido 3-(3,5-Dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**514**, 15.0 mg, 0.046 mmol) al disolver en diclorometano (10.0 ml) al cual se agregó ácido trifluoroacético (0.10 ml, 1.3 mmol). La reacción se agitó a temperatura ambiente

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durante 1 hora, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y lavó con acetato de etilo en hexano para dar un sólido blanquecino (**P-0124**, 7.5 mg, 72.0%). MS (ESI) $[M+H^+]^+$ = 227.3.

[0119] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 158, reemplazando dimetil-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-amina **2** con (5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-dimetil-amina (preparada como se describe en el Ejemplo 10, Esquema 164, aislada después de la etapa 1) en la Etapa 1 y reemplazando isocianato de bencilo con un electrófilo apropiado en la Etapa 5. Los siguientes compuestos se produjeron siguiendo este procedimiento:

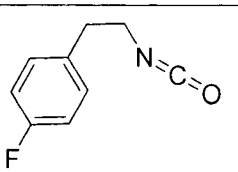
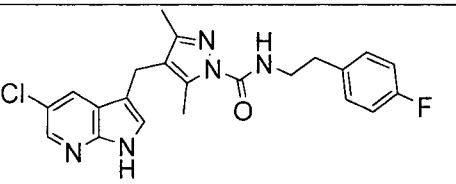
[2-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico (**P-0157**),

4-fluoro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico (**P-0158**),

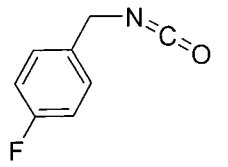
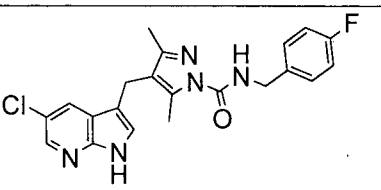
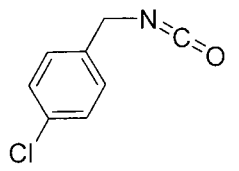
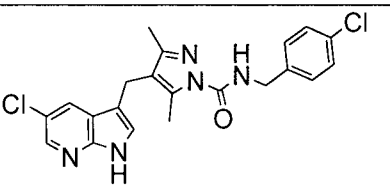
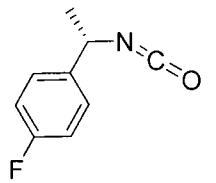
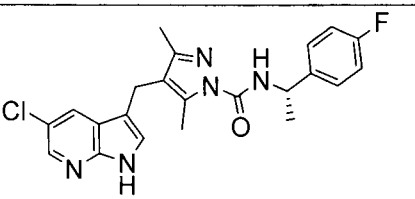
4-cloro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico (**P-0159**), y

[(S)-1-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico (**P-0160**).

[0120] El electrófilo usado en lugar de isocianato de bencilo en la Etapa 5 se indica en la Columna 2 de la siguiente tabla, con la estructura del compuesto dada en la Columna 3. La Columna 1 proporciona el número de compuesto y la Columna 4 el resultado experimental de la espectrometría de masas.

	Electrófilo	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0157			426.2

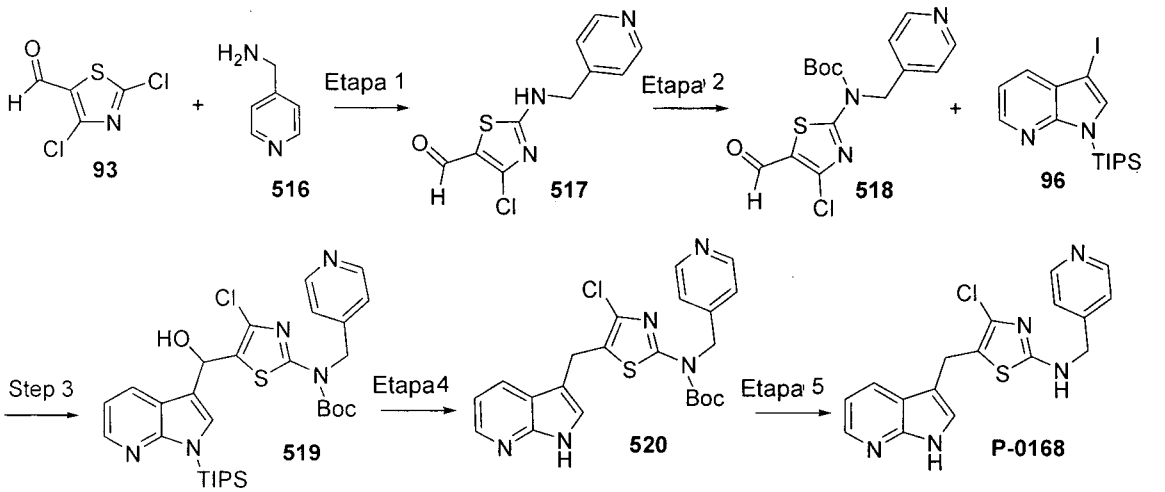
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P-0158			412.2
P-0159			428.2
P-0160			426.2

Ejemplo 5: Síntesis de [4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina P-0168

[0121] [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina **P-0168** se sintetizó en 5 etapas como se muestra en el Esquema 159.

Esquema 159



*Etapa 1 – Preparación de 4-cloro-2-[(piridin-4-ilmetil)-amino]-tiazol-5-carbaldehído (**517**):*

[0122] A una solución de 4-(aminometil)piridina (**516**, 1.16 ml, 11.5 mmol) y N,N-diisopropiletilamina (3.8 ml, 22 mmol) en tetrahidrofurano (50 ml) se agregó 2,4-dicloro-tiazol-5-

carbaldehído (**93**, 2.0 g, 11.0 mmol) en tetrahidrofurano (5 ml) 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, y se secó sobre sulfato de sodio. El compuesto sin purificar 4-cloro-2-[(piridin-4-ilmetil)-amino]-tiazol-5-carbaldehído (**517**) se usó para la siguiente etapa sin purificación.

*Etapa 2 – Preparación de ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-piridin-4-ilmetil-carbámico (**518**):*

[0123] Una mezcla de 4-cloro-2-[(piridin-4-ilmetil)-amino]-tiazol-5-carbaldehído (**517**, 3.28 g, 11.0 mmol), di-ter-butildicarbonato (4.0 g, 18 mol) y trietilamina (10 ml, 74 mmol) en diclorometano (120 ml) se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo en hexanos para proporcionar el compuesto deseado como un sólido amarillo (**518,** 564 mg, 15%). MS (ESI) $[M+H^+]^+$ = 354.1.

*Etapa 3 – Preparación de ter-butiléster del ácido {4-cloro-5-[hidroxi-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-tiazol-2-il}-piridin-4-ilmetil-carbámico (**519**):*

[0124] A una solución de 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**96**, 0.44 g, 1.1 mmol) en tetrahidrofurano (20 ml) a -20 °C, cloruro de isopropilmagnesio (2 M en tetrahidrofurano, 0.6 ml, 1.2 mmol) se agregó por goteo. La mezcla de reacción se dejó entibiar a 0 °C en 10 minutos. La mezcla de reacción luego se enfrió a -40 °C. Una solución de ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-piridin-4-ilmetil-carbámico (**518**, 0.26 g, 0.73 mmol) en tetrahidrofurano (4 ml) se agregó a la mezcla de reacción. La mezcla de reacción se dejó entibiar a -10 °C durante 30 minutos. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo en hexanos para proporcionar el compuesto deseado como un sólido amarillo (**519**, 397 mg, 86%). MS (ESI) $[M+H^+]^+$ = 628.3.

Etapa 4 – Preparación de ter-butiléster del ácido [4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-

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*2-il]-piridin-4-ilmetil-carbámico (**520**):*

[0125] Una mezcla de ter-butiléster del ácido {4-cloro-5-[hidroxi-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-tiazol-2-il}-piridin-4-ilmetil-carbámico (**519**, 0.397 g, 0.57 mmol), trietilsilano (1.0 ml, 6.3 mmol), y ácido trifluoroacético (0.5 ml, 6 mmol) en acetonitrilo (10 ml) se agitó a 40 °C durante 2 horas. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con bicarbonato de sodio, se lavó con salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con metanol en diclorometano para proporcionar el compuesto deseado como un sólido amarillo (**520**, 126 mg, 49%). MS (ESI) $[M+H^+]^+ = 456.2$.

*Etapa 5 – Preparación de [4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina (**P-0168**):*

[0126] A una solución de ter-butiléster del ácido [4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-carbámico (**520**, 126 mg, 0.000276 mol) en diclorometano (2 ml) se agregó cloruro de hidrógeno (4 M en 1,4-dioxano, 2 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se vertió en solución fría de bicarbonato de sodio, se extrajo con acetato de etilo, se lavó con salmuera y se secó sobre sulfato de magnesio. Después de la remoción de los solventes, el residuo se lavó con acetato de etilo para proporcionar el compuesto deseado como un sólido amarillo claro (**P-0168**, 68.4 mg, 70%). MS (ESI) $[M+H^+]^+ = 356.2$.

[0127] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 159, reemplazando 4-(aminometil)piridina **516** con una amina apropiada. Los siguientes compuestos se produjeron siguiendo este procedimiento:

[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]-piridin-2-ilmetil-amina (**P-0167**),

[4-Cloro-5-(1H-pirrolo[2,3-*b*]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina (**P-0171**),

[4-Cloro-5-(1H-pirrolo[2,3-*b*]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-0173**),

[4-Cloro-5-(1H-pirrolo[2,3-*b*]piridin-3-ilmetil)-tiazol-2-il]-(1,5-dimetil-1H-pirazol-3-ilmetil)-amina

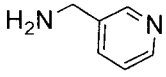
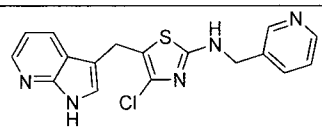
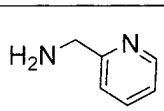
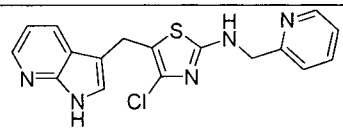
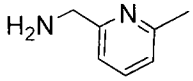
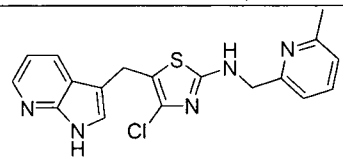
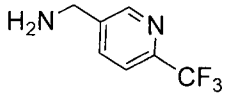
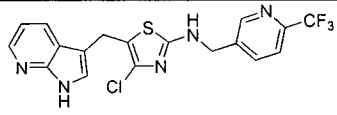
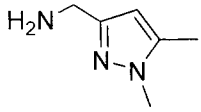
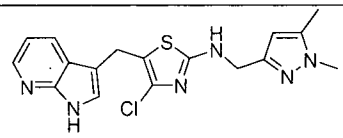
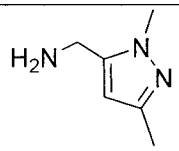
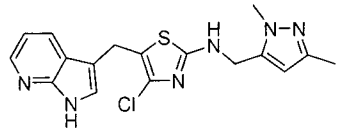
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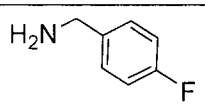
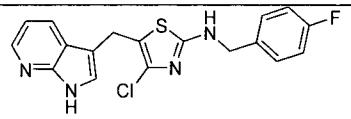
[4-Cloro-5-(1H-pirrolo[2,3-*b*]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-2H-pirazol-3-ilmetil)-amina (**P-0175**), y

[4-Cloro-5-(1H-pirrolo[2,3-*b*]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina (**P-0156**).

La siguiente tabla indica la amina (Columna 2) usada en el Esquema 159 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 la masa observada.

Número de compuesto	Amina	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0164			356.1
P-0167			356.1
P-0171			370.2
P-0173			424.2
P-0172			373.2
P-0175			373.2

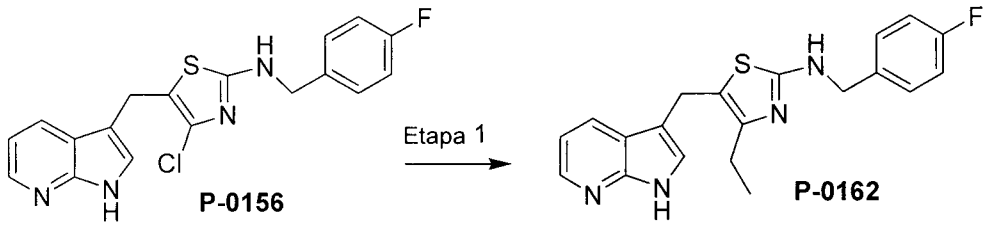
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Número de compuesto	Amina	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0156			373.1

Ejemplo 6: Síntesis de [4-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina P-0162 y (4-fluoro-bencil)-[4-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina P-0162

[0128] [4-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **P-0162** se sintetizó en 1 etapa a partir de [4-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **P-0156** como se muestra en el Esquema 160.

Esquema 160

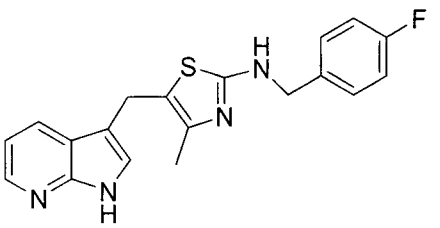


*Etapa 1 – Preparación de [4-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina (**P-0162**):*

[0129] En un matraz de fondo redondo, bajo una atmósfera de nitrógeno, [1,1'-bis(difenilfosfino) ferroceno] dicloro paladio (II), en complejo con diclorometano (1:1), se colocó con tolueno (15 ml, 140 mmol). [4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina (**P-0156**,145 mg, 0.4 mmol) se agregó en 5 ml de tolueno a temperatura ambiente. La mezcla se agitó durante 10 minutos. A la reacción en agitación, una solución de bromuro de etilmagnesio 3.13 M en éter (1.86 ml) se agregó por goteo a temperatura ambiente. La solución opaca se calentó a 60 °C. Tetrahidrofurano (10 ml) se agregó a la solución tibia. La mezcla se calentó a reflujo durante dos horas adicionales. Después de enfriar a 0 °C, la reacción se extinguió con una solución de ácido cítrico a pH 4-5 en hielo-agua y se agitó a temperatura ambiente. La mezcla se diluyó con acetato

de etilo y se lavó con bicarbonato de sodio saturado y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y el solvente se removió bajo presión reducida. La purificación con cromatografía instantánea, eluyendo con un gradiente de acetato de etilo:hexanos (20:100), dio un sólido amarillo que se lavó además con acetato de etilo para dar **P-0162** (15 mg,10%) como un sólido blanquecino. MS (ESI) $[M+H^+]^+$ = 367.2.

[0130] (4-fluoro-bencil)-[4-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **P-0163**

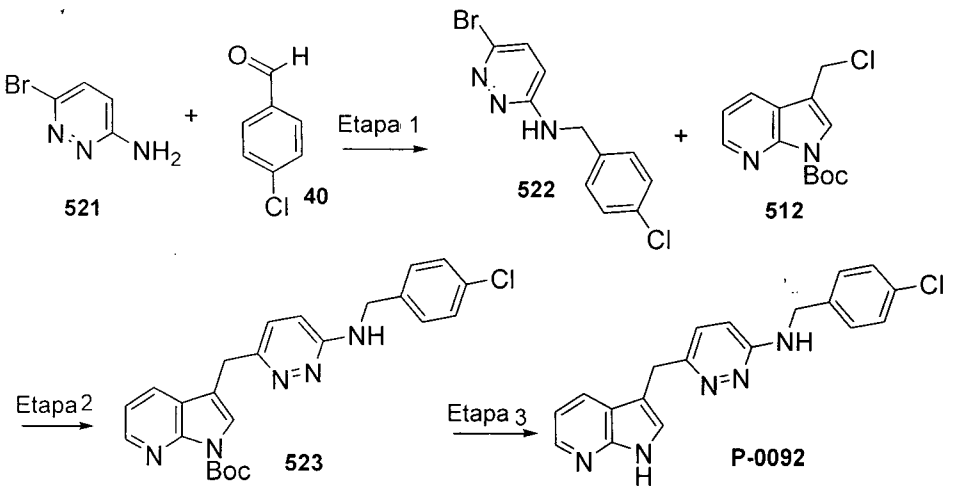


se preparó usando el protocolo del Esquema 160, sustituyendo el bromuro de etilmagnesio 3.13 M en solución de éter con 1.4 M de bromuro de metilmagnesio en tetrahidrofurano. MS (ESI) $[M+H^+]^+$ = 353.2.

Ejemplo 7: Síntesis de (4-Cloro-bencil)-[6-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridazin-3-il]-amina P-0092

[0131] (4-Cloro-bencil)-[6-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridazin-3-il]-amina **P-0092** se sintetizó en 3 etapas como se muestra en el Esquema 161.

Esquema 161



*Etapa 1 – Síntesis de (6-bromo-piridazin-3-il)-(4-cloro-bencil)-amina (**522**):*

[0132] A 6-bromo-piridazin-3-ilamina (**521**, 0.85 g, 0.0049 mol) en acetonitrilo (30.0 ml) se

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agregaron 4-clorobenzaldehído (**40**, 0.82 g, 0.0058 mol), trietilsilano (4.0 ml, 0.025 mol) y ácido trifluoroacético (2.0 ml, 0.026 mol). La reacción se calentó a reflujo durante 4 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 anhidro, y se filtró. El filtrado se concentró y lavó con acetato de etilo para dar un sólido blanco (**522**, 1.0 g). MS (ESI) $[M+H^+]^+ = 298.3, 300.2$.

*Etapa 2 – Preparación de ter-butiléster del ácido 3-[6-(4-cloro-bencilamino)-piridazin-3-ilmetil]-pirrolo[2,3-b]piridina-1-carboxílico (**523**):*

[0133] A (6-bromo-piridazin-3-il)-(4-cloro-bencil)-amina (**522**, 0.560 g, 1.88 mmol) en tetrahidrofurano (45.0 ml), bajo una atmósfera de nitrógeno a -78 °C, se agregó n-butilitio (2.50 M en hexano, 0.760 ml) lentamente. Después de 10 minutos, 1,2-bis-(cloro-dimetil-silanil)-etano (0.201 g, 0.94 mmol) en tetrahidrofurano (5.0 ml) se agregó a la reacción. La mezcla de reacción se dejó agitar a temperatura ambiente durante 3 horas. La reacción se enfrió a -78 °C, seguido por adición de 1.70 M de ter-butilitio en hexano (1.20 ml) lentamente. La reacción se agitó durante 20 minutos, seguido por adición de una solución de CuCN.2LiCl (0.6 M en tetrahidrofurano, 3.00 ml) y ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**512**, 0.47 g, 1.8 mol) en tetrahidrofurano (10.0 ml). Después de 30 minutos, la reacción se dejó entibiar a temperatura ambiente durante 10 minutos. La reacción 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 trató con ácido trifluoroacético (1.0 ml) disuelto en diclorometano (10.0 ml) durante 10 minutos. La reacción 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 y se filtró. El filtrado se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 60% de acetato de etilo en hexano para dar el compuesto deseado (**523**, 0.10 g, 23.8%). MS (ESI) $[M+H^+]^+ = 450.1$.

*Etapa 3 – Preparación de (4-cloro-bencil)-[6-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridazin-3-il]-amina (**P-0092**):*

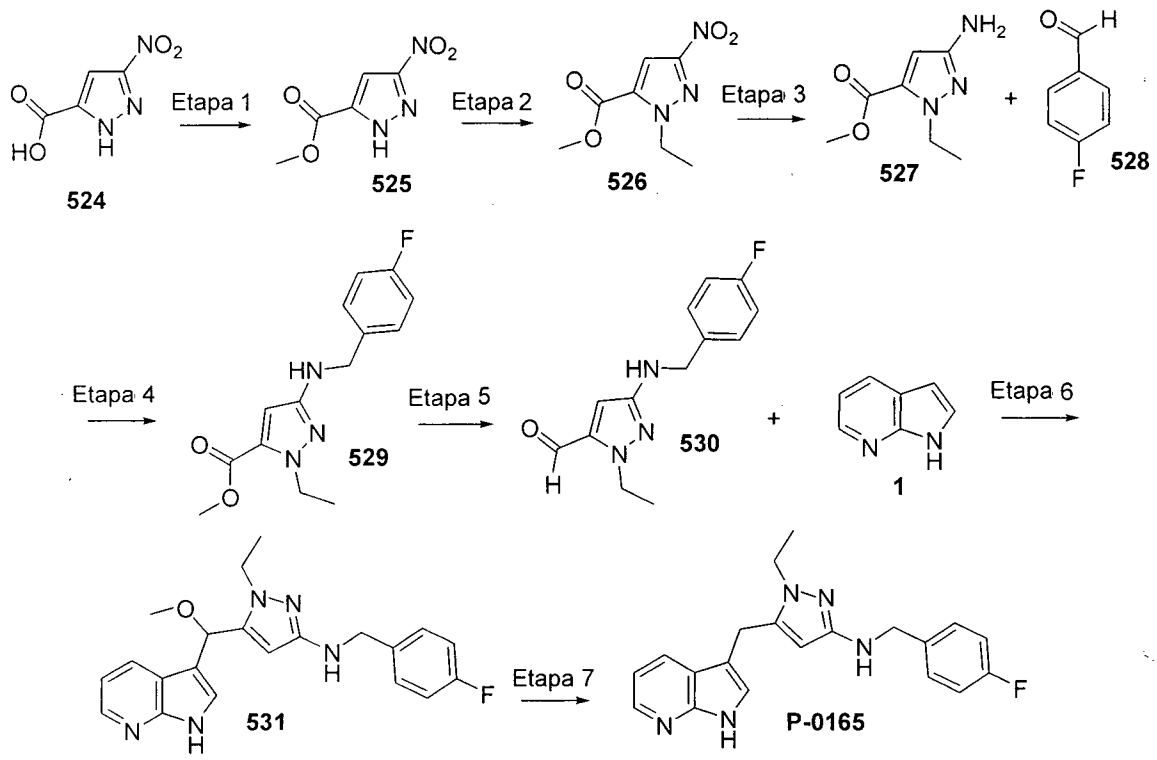
[0134] A ter-butiléster del ácido 3-[6-(4-cloro-bencilamino)-piridazin-3-ilmetil]-pirrolo[2,3-b]piridina-1-carboxílico (**523**, 50.0 mg, 0.111 mmol) en diclorometano (10.0 ml) se agregó ácido trifluoroacético (0.30 ml, 0.0039 mol). La reacción se agitó a temperatura ambiente durante la noche. La reacción

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 y se filtró. El filtrado se concentró y lavó con acetato de etilo y hexano para dar un sólido blanquecino (**P-0092**, 7.3 mg, 19.0%). MS (ESI) $[M+H^+]^+$ = 350.1.

Ejemplo 8: Síntesis de [1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina P-0165

[0135] [1-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **P-0165** se sintetizó en 7 etapas como se muestra en el Esquema 162.

Esquema 162



*Etapa 1 – Preparación de metiléster del ácido 5-nitro-2H-pirazol-3-carboxílico (**525**):*

[0136] A ácido 5-nitro-2H-pirazol-3-carboxílico (**524**, 10.0 g, 0.0637 mol) en metanol (100.0 ml) se agregó ácido sulfúrico concentrado (1.00 ml, 0.0180 mol). La reacción se agitó a temperatura ambiente durante la noche. 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 anhidro y se filtró. El filtrado se

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concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano para dar un sólido blanco (**525**, 1.5 g, 13.8%).

*Etapa 2 – Preparación de 2-etil-metiléster del ácido 5-nitro-2H-pirazol-3-carboxílico (**526**):*

[0137] A metiléster del ácido 5-nitro-2H-pirazol-3-carboxílico (**525**, 2.50 g, 0.0146 mol) en N,N-dimetilformamida (62.5 ml) se agregaron yodoetano (1.2 ml, 0.016 mol) y carbonato de potasio (4.17 g, 0.0301 mol) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante la noche. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**526**, 1.3 g, 44.7%).

*Etapa 3 – Preparación de metiléster del ácido 5-amino-2-etil-2H-pirazol-3-carboxílico (**527**):*

[0138] A 2-etil-metiléster del ácido 5-nitro-2H-pirazol-3-carboxílico (**526**, 1.30 g, 6.53 mmol) en metanol (60.0 ml) se agregó 20% de $Pd(OH)_2/C$ (0.1 g). La reacción se agitó bajo una atmósfera de hidrógeno durante la noche. La reacción se filtró y concentró para dar un sólido amarillo claro (**527**, 1.0 g, 90.6%).

*Etapa 4 – Preparación de metiléster del ácido 2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-carboxílico (**529**):*

[0139] A metiléster del ácido 5-amino-2-etil-2H-pirazol-3-carboxílico (**527**, 1.00 g, 5.91 mmol) en acetonitrilo (27.5 ml) se agregaron 4-fluorobenzaldehído (**528**, 0.660 ml, 6.26 mmol), trietilsilano (4.77 ml, 0.0298 mol) y ácido trifluoroacético (2.38 ml, 0.0310 mol). La reacción se agitó a 80 °C durante 4 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 y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**529**, 1.00 g, 61%).

*Etapa 5 – Preparación de 2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-carbaldehído (**530**):*

[0140] A metiléster del ácido 2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-carboxílico (**529**, 1.00 g, 3.61 mol) en tetrahidrofurano (70.0 ml) bajo una atmósfera de nitrógeno a temperatura ambiente, tetrahidroaluminato de litio (1.00 M en tetrahidrofurano, 10.00 ml) se agregó lentamente. La

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reacción se agitó a temperatura ambiente durante la noche, seguido por agregar lentamente sulfato de sodio decahidratado (15.0 g). Después de 2 horas, la reacción se filtró, concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un aceite amarillo (**530**, 0.16 g, 18%). MS (ESI) $[M+H^+]^+$ = 248.2.

*Etapa 6 – Preparación de 1-etil-5-[metoxi-(1H-pirrolo[2,3-b]piridin-3-il)-metil]-1H-pirazol-3-il-(4-fluoro-bencil)-amina (**531**):*

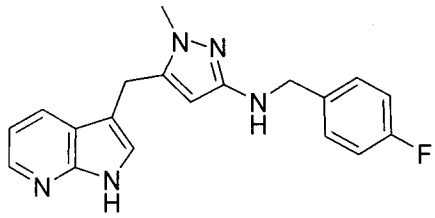
[0141] A 1H-Pirrolo[2,3-b]piridina (**1**, 54.0 mg, 0.46 mmol) en metanol (15.0 ml) se agregaron 2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-carbaldehído (**530**, 110.0 mg, 0.44 mmol) e hidróxido de potasio (0.60 g, 0.011 mol) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 40% de acetato de etilo en hexano para dar un sólido blanco (**531**, 0.12 g, 71.1%). MS (ESI) $[M-H^+]^-$ = 378.2.

*Etapa 7 – Preparación de [1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**P-0165**):*

[0142] A 1-etil-5-[metoxi-(1H-pirrolo[2,3-b]piridin-3-il)-metil]-1H-pirazol-3-il-(4-fluoro-bencil)-amina (**531**, 0.12 g, 0.32 mmol) en acetonitrilo (10.0 ml, 0.191 mol) se agregaron trietilsilano (0.60 ml, 0.0038 mol) y ácido trifluoroacético (0.30 ml, 0.0039 mol). La reacción se agitó a 80 °C durante 2 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 anhidro y se filtró. El filtrado se concentró y lavó con acetato de etilo y hexano para dar el compuesto sin purificar. La ^1H NMR indicó que la reacción fue incompleta. El compuesto sin purificar se disolvió en diclorometano (15.0 ml), ácido trifluoroacético (0.30 ml) y trietilsilano (0.60 ml). La reacción se agitó a 43 °C durante 72 horas. La reacción 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 y se filtró. El filtrado se concentró y lavó con acetato de etilo y hexano para dar un sólido blanquecino (**P-0165**, 18.7 mg, 17%). MS (ESI) $[M+H^+]^+$ = 350.3.

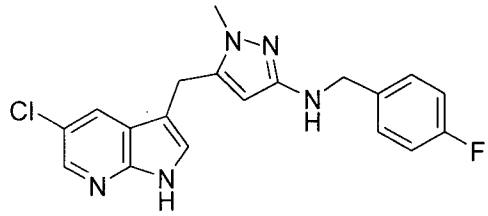
[0143] (4-fluoro-bencil)-[1-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-amina **P-0169**

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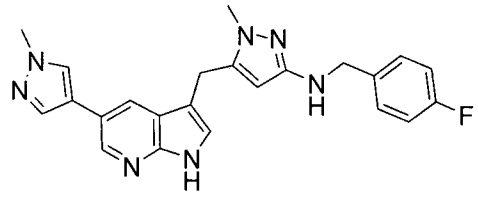
se preparó usando el protocolo del Esquema 162, sustituyendo yodoetano con yodometano en la Etapa 2. MS (ESI) $[M+H^+]^+$ = 336.3.

[0144] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina **P-0170**



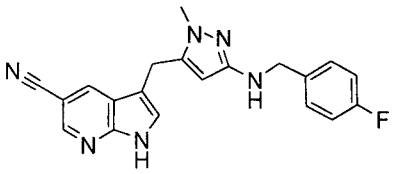
se preparó usando el protocolo del Esquema 162, sustituyendo yodoetano con yodometano en la etapa 2 y 1H-pirrolo[2,3-b]piridina **1** con 5-cloro-1H-pirrolo[2,3-b]piridina en la etapa 6. MS (ESI) $[M+H^+]^+$ = 370.3

[0145] (4-fluoro-bencil)-{1-metil-5-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-1H-pirazol-3-il}-amina **P-0180**



se preparó usando el protocolo del Esquema 162, sustituyendo yodoetano con yodometano en la etapa 2 y 1H-Pirrolo[2,3-b]piridina **1** con 5-(1-Metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina (preparada como se describe en el Ejemplo 18, Esquema 172) en la etapa 6. MS (ESI) $[M+H^+]^+$ = 416.2.

[0146] 3-[5-(4-fluoro-bencilamino)-2-metil-2H-pirazol-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo **P-0191**

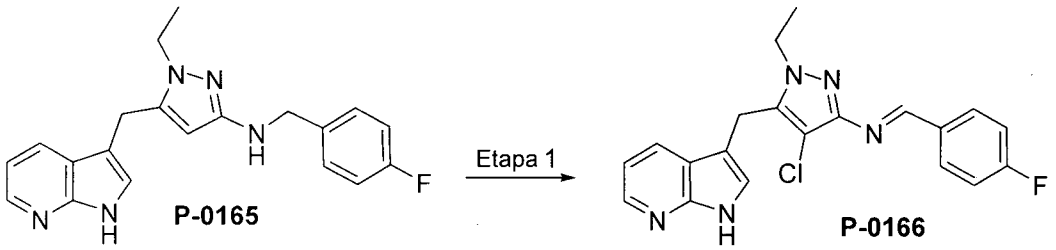


se preparó usando el protocolo del Esquema 162, sustituyendo 1H-Pirrolo[2,3-b]piridina **1** con 1H-Pirrolo[2,3-b]piridina-5-carbonitrilo en la Etapa 6. MS (ESI) $[M+H^+]^+$ = 361.5.

Ejemplo 9: Síntesis de [4-cloro-1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-[1-(4-fluoro-fenil)-met-(E)-ilideno]-amina P-0166

[0147] [4-cloro-1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-[1-(4-fluoro-fenil)-met-(E)-ilideno]-amina **P-0166** se sintetizó en 1 etapa como se muestra en el Esquema 163.

Esquema 163



*Etapa 1 – Preparación de [4-cloro-1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-[1-(4-fluoro-fenil)-met-(E)-ilideno]-amina (**P-0166**):*

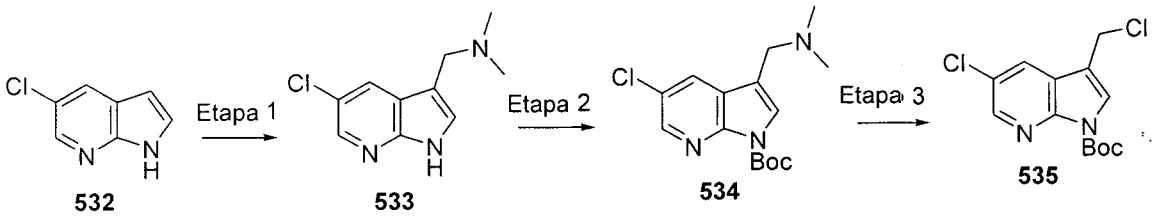
[0148] A [1-etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**P-0165**, 10.1 mg, 0.0289 mmol, preparada como se describe en el Ejemplo 8, Esquema 162) en acetonitrilo (8.0 ml) se agregó N-cloro-succinimida (4.18 mg, 0.0318 mmol). La reacción se agitó a temperatura ambiente durante 2 horas. La reacción se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**P-0166**, 1.1 mg). MS (ESI) $[M+H^+]^+$ = 382.1.

Ejemplo 10: Síntesis de 5-cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico

[0149] 5-cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico se sintetizó en 3 etapas como se muestra en el Esquema 164.

Esquema 164

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532 **533** **534** **535**

*Etapa 1 – Preparación de (5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-dimetil-amina (**533**):*

[0150] A 5-Cloro-1H-pirrolo[2,3-b]piridina (**532**, 8.00 g, 0.0524 mol) en alcohol isopropílico (250.0 ml) se agregaron clorhidrato de dimetilamina (4.79 g, 0.0587 mol) y formaldehído (1.77 g, 0.0589 mol). 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 (**533**, 10.0 g, 91%), que se usó directamente en la siguiente etapa.

*Etapa 2 y 3 – Preparación de 5-cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**535**):*

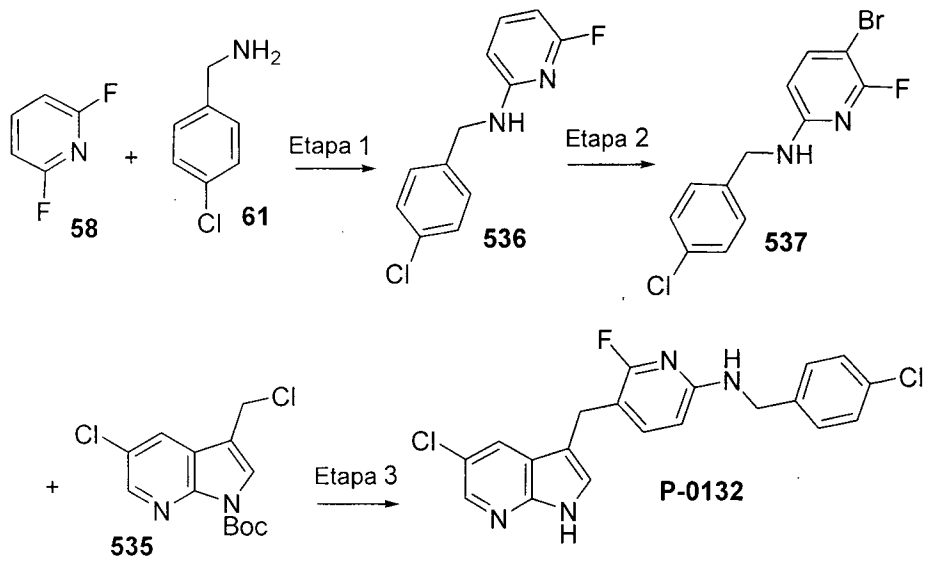
[0151] 5-Cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico **535** se preparó siguiendo el protocolo del Esquema 158 (Ejemplo 4) etapas 1 y 2, sustituyendo dimetil-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-amina **2** con (5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-dimetil-amina **533** en la etapa 1.

Ejemplo 11: Síntesis de (4-cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina P-0132

[0152] (4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina **P-0132** se sintetizó en 3 etapas como se muestra en el Esquema 165.

Esquema 165

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*Etapa 1 –Preparación de (4-cloro-bencil)-(6-fluoro-piridin-2-il)-amina (**536**):*

[0153] A 2,6-difluoropiridina (**58**, 9.85 g, 0.0856 mol) en N-metilpirrolidinona (50.0 ml) se agregaron p-clorobencilamina (**61**, 10.5 ml, 8.63 mmol) y N,N-diisopropiletilamina (30.0 ml, 0.172 mol). La reacción se agitó a 90 °C durante la noche. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 25% de acetato de etilo en hexano, luego se lavó con acetato de etilo/hexano para dar un sólido blanco (**536**, 10 g, 50%).

*Etapa 2 – Preparación de (5-bromo-6-fluoro-piridin-2-il)-(4-cloro-bencil)-amina (**537**):*

[0154] A (4-cloro-bencil)-(6-fluoro-piridin-2-il)-amina (**536**, 1.03 g, 4.35 mmol) en acetonitrilo (30.0 ml), bajo una atmósfera de nitrógeno, N-bromosuccinimida (0.820 g, 4.61 mol) se agregó lentamente. Después de 2 horas, la reacción se vertió en una solución de tiosulfato de sodio y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se concentró y cristalizó con acetato de etilo y hexano para dar un sólido blanco (**537**, 1.10 g, 80.1%).

*Etapa 3 – Preparación de (4-cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina (**P-0132**):*

[0155] A (5-bromo-6-fluoro-piridin-2-il)-(4-cloro-bencil)-amina (**537**, 2.76 g, 8.75 mol) en tetrahidrofurano (90.0 ml), bajo una atmósfera de nitrógeno a -78 °C, n-butilitio (2.50 M en hexano, 3.64 ml) se agregó lentamente. Después de 60 minutos, 1,2-bis-(cloro-dimetil-silanil)-etano (0.942 g, 4.38 mol) en tetrahidrofurano (8.0 ml) se agregó a la reacción. La mezcla de reacción se dejó

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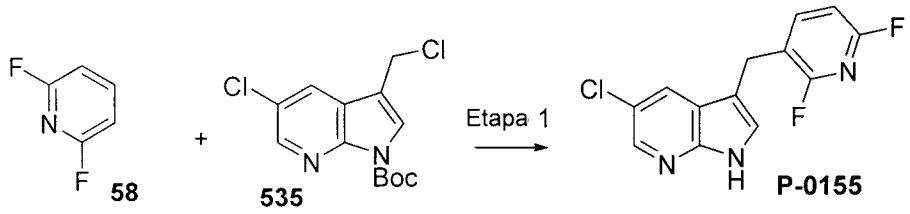
agitar a temperatura ambiente durante 2 horas. La reacción se enfrió a -78 °C, seguido por adición de ter-butilitio (1.70 M en hexano, 10.50 ml). La reacción se agitó durante 30 minutos, seguido por adición de 0.65 M de CuCN.2LiCl en tetrahidrofurano (14.0 ml). La reacción se agitó a -35 °C durante 10 minutos, seguido por adición de 5-cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**535**, 1.70 g, 5.64 mol, preparado como se describe en el Ejemplo 10, Esquema 164) en tetrahidrofurano (10.0 ml). La reacción se dejó entibiar a temperatura ambiente durante 1 hora y 2 N HCl (30 ml) se agregó a la mezcla de reacción, luego se agitó durante 30 minutos. La reacción se vertió en amoniaco acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 30% de acetato de etilo en hexano para dar el compuesto deseado (**P-0132**, 0.75 g, 33.1%). MS (ESI) $[M+H^+]^+$ = 401.1.

Etapa

Ejemplo 12: Síntesis de 5-cloro-3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina P-0155

[0156] 5-Cloro-3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina **P-0155** se sintetizó en 1 etapa como se muestra en el Esquema 166.

Esquema 166



*Etapa 1 – Preparación de 5-cloro-3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina (**P-0155**):*

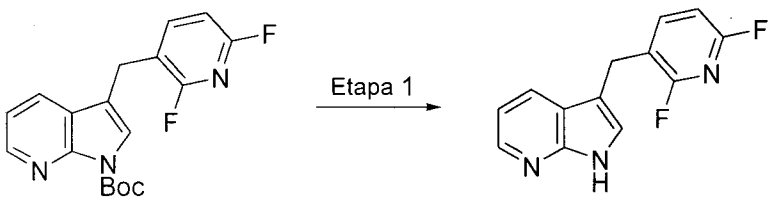
[0157] A 2,6-Difluoropiridina (**58**, 3.40 g, 0.0295 mol) en tetrahidrofurano (200.0 ml), bajo una atmósfera de nitrógeno a -78 °C, 2.50 M de n-butilitio en hexano (12.0 ml) se agregó lentamente. Después de 60 minutos, CuCN.2LiCl (0.75 M en tetrahidrofurano, 40.0 ml) se agregó a la mezcla de reacción. Después de 5 minutos, 5-cloro-ter-butiléster del ácido 3-Clorometil-pirrolo[2,3-b]piridina-1-carboxílico (**535**, 4.20 g, 0.0139 mol, preparado como se describe en el Ejemplo 10, Esquema 164) en tetrahidrofurano (20 ml) se agregó a la reacción. La reacción se agitó a -78 °C durante la noche, luego se vertió en agua y amoniaco (10 ml), y se extrajo con acetato de etilo. La

capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 15% de acetato de etilo en hexano para dar un sólido blanco (**P-0155**, 300 mg, 7.7%). MS (ESI) $[M-H^+]^-$ = 278.1.

Ejemplo 13: Síntesis de 3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina P-0154

[0158] 3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina **P-0154** se sintetizó en 1 etapa como se muestra en el Esquema 167.

Esquema 167



536 **P-0154**

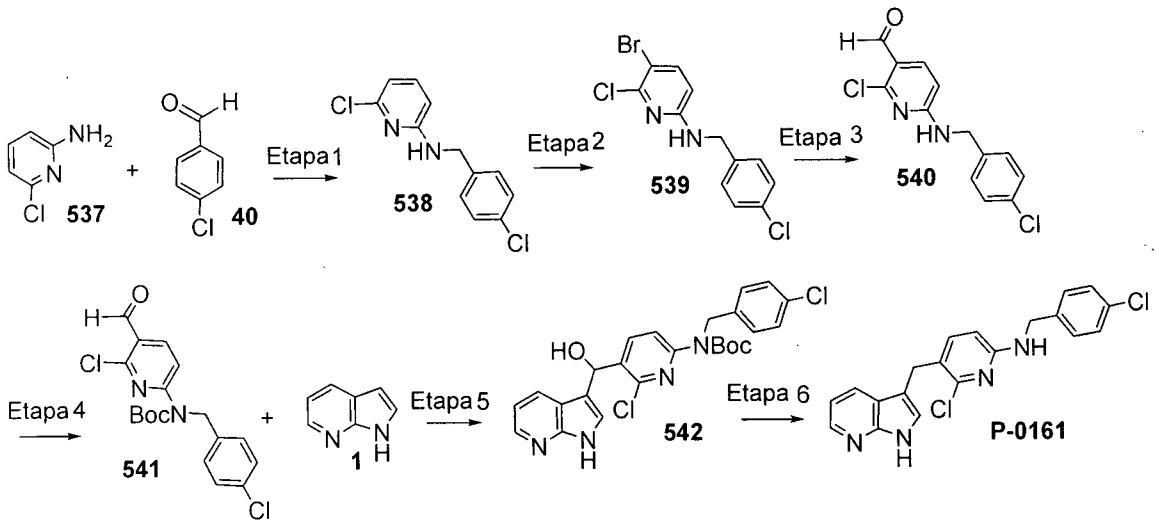
*Etapa 1 – Preparación de 3-(2,6-difluoro-piridin-3-ilmetil)-1H-pirrolo[2,3-b]piridina (**P-0154**):*

[0159] A ter-butiléster del ácido 3-(2,6-difluoro-piridin-3-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**536**, 0.35 g, 1.0 mmol, preparado como se describe en el Ejemplo 10, Esquema 164, reemplazando 5-cloro-1H-pirrolo[2,3-b]piridina **532** con 1H-pirrolo[2,3-b]piridina en la etapa 1) en N-metilpirrolidinona (3.00 ml) se agregaron p-clorobencilamina (0.20 ml, 1.6 mmol) y N,N-diisopropiletilamina (0.30 ml, 0.0017 mol). La reacción se agitó a 50 °C durante 72 horas. La reacción 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 y el intermediario sin purificar se disolvió en diclorometano (15.0 ml) y ácido trifluoroacético (0.5 ml). La reacción se agitó a temperatura ambiente durante 2 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 y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 35% de acetato de etilo en hexano para dar un sólido blanco (**P-0154**, 0.18 g, 72%). MS (ESI) $[M+H^+]^+$ = 246.2.

Ejemplo 14: Síntesis de 5-((1H-pirrolo[2,3-b]piridin-3-il)metil)-N-(4-clorobencil)-6-cloropiridin-2-amina P-0161

[0160] 5-((1H-pirrolo[2,3-b]piridin-3-il)metil)-N-(4-clorobencil)-6-cloropiridin-2-amina **P-0161** se sintetizó en 6 etapas como se muestra en el Esquema 168.

Esquema 168



*Etapa 1 - Preparación de (4-cloro-bencil)-(6-cloro-piridin-2-il)-amina (**538**):*

[0161] A 6-cloro-piridin-2-ilamina (**537**, 5.60 g, 0.0436 mol) en acetonitrilo (300 ml) se agregaron 4-clorobenzaldehído (**40**, 6.7 g, 0.048 mol), ácido trifluoroacético (13 ml, 0.17 mol) y trietilsilano (21 ml, 0.13 mol). La reacción se calentó a reflujo durante 4 horas, luego se concentró, se vertió en agua, se extrajo con acetato de etilo, y se lavó con bicarbonato de sodio y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró y concentró. El filtrado se purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**538**, 6.5 g, 59%). MS (ESI) $[M+H^+]^+$ = 255.1.

*Etapa 2 – Preparación de (5-bromo-6-cloro-piridin-2-il)-(4-cloro-bencil)-amina (**539**):*

[0162] A (4-cloro-bencil)-(6-cloro-piridin-2-il)-amina (**538**, 4.00 g, 0.0158 mol) en acetonitrilo (66.7 ml, 1.28 mol) bajo una atmósfera de nitrógeno, N-bromosuccinimida (2.81 g, 0.0158 mol) en acetonitrilo (20 ml) se agregó lentamente. 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 concentró y cristalizó con acetato de etilo en hexano para dar un sólido blanco (**539**, 2.60 g, 95.3%).

*Etapa 3 – Preparación de 2-cloro-6-(4-cloro-bencilamino)-piridina-3-carbaldehído (**540**):*

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[0163] A (5-bromo-6-cloro-piridin-2-il)-(4-cloro-bencil)-amina (**539**, 2.60 g, 7.83 mmol) en tetrahidrofurano (60.0 ml) bajo una atmósfera de nitrógeno a -78 °C, cloruro de isopropilmagnesio (2.00 M en tetrahidrofurano, 4.20 ml) se agregó durante 10 minutos. La reacción se agitó a -78 °C durante 20 minutos, luego se dejó entibiar a temperatura ambiente durante 10 minutos. La reacción se enfrió a -78 °C. ter-Butilitio (1.70 M en hexano, 10.2 ml) se agregó a la reacción durante 10 minutos. Después de 40 minutos, N,N-dimetilformamida (1.80 ml, 0.0232 mol) se agregó a la reacción. La reacción se agitó a -78 °C durante 40 minutos, luego se dejó entibiar a temperatura ambiente durante otros 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 concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 35% a 100% de acetato de etilo en hexano para dar un sólido amarillo claro (**540**, 1.0 g, 45.4%). MS (ESI) $[M-H^+]^-$ = 279.0.

*Etapa 4 – Preparación de ter-butiléster del ácido (4-cloro-bencil)-(6-cloro-5-formil-piridin-2-il)-carbámico (**541**):*

[0164] A 2-cloro-6-(4-cloro-bencilamino)-piridina-3-carbaldehído (**540**, 0.40 g, 1.42 mmol) en diclorometano (10.0 ml) se agregaron 4-dimetilaminopiridina (10.0 mg, 0.082 mmol), di-ter-butildicarbonato (0.693 g, 3.17 mmol) y trietilamina (0.50 ml, 0.0036 mol). La reacción se agitó a temperatura ambiente durante la noche, luego se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**541**, 0.45 g, 83.0%).

*Etapa 5 – Preparación de ter-butiléster del ácido (4-cloro-bencil)-6-cloro-5-[hidroxi-(1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il-carbámico (**542**):*

[0165] A 1H-Pirrolo[2,3-b]piridina (**1**, 465 mg, 3.93 mmol) en metanol (50 ml) se agregaron hidróxido de sodio (0.630 g, 0.0157 mol) y ter-butiléster del ácido (4-cloro-bencil)-(6-cloro-5-formil-piridin-2-il)-carbámico (**541**, 1.5 g, 0.0039 mol). 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 lavó con salmuera, se secó sobre sulfato de sodio, se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el

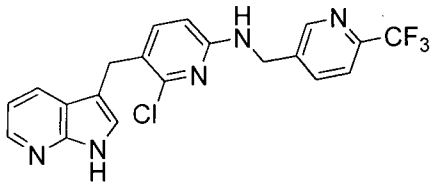
302

compuesto deseado (**542**, 1.0g, 51%). MS (ESI) $[M+H^+]^+$ = 499.1.

*Etapa 6 – Preparación de 5-((1H-pirrolo[2,3-b]piridin-3-il)metil)-N-(4-clorobencil)-6-cloropiridin-2-amina (**P-0161**):*

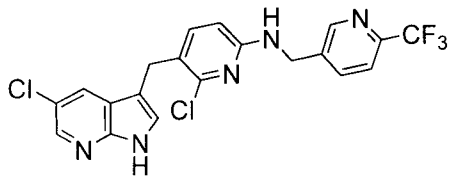
[0166] A ter-butiléster del ácido (4-cloro-bencil)-6-cloro-5-[hidroxi-(1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il-carbámico (**542**, 1.00 g, 2.00 mmol) en acetonitrilo (130.0 ml) se agregaron trietilsilano (11.5 ml, 0.0720 mol) y ácido trifluoroacético (5.5 ml, 0.071 mol). La reacción se calentó a reflujo durante 2 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 y se filtró. El filtrado se concentró y lavó con acetato de etilo y hexano para dar un sólido amarillo claro (**P-0161**, 480 mg, 62%). MS (ESI) $[M+H^+]^+$ = 383.1, 385.1.

[0167] [6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-0174**



se preparó siguiendo el protocolo del Esquema 168, sustituyendo 4-cloro-benzaldehído **40** con 6-trifluorometil-piridina-3-carbaldehído en la etapa 1. MS (ESI) $[M+H^+]^+$ = 418.2.

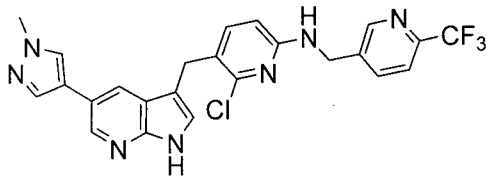
[0168] [6-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-0176**



se preparó siguiendo el protocolo del Esquema 168, sustituyendo 4-cloro-benzaldehído **40** con 6-trifluorometil-piridina-3-carbaldehído en la etapa 1 y 1H-Pirrolo[2,3-b]piridina **1** con 5-cloro-1H-pirrolo[2,3-b]piridina en la etapa 5. MS (ESI) $[M+H^+]^+$ = 452.0.

[0169] {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**

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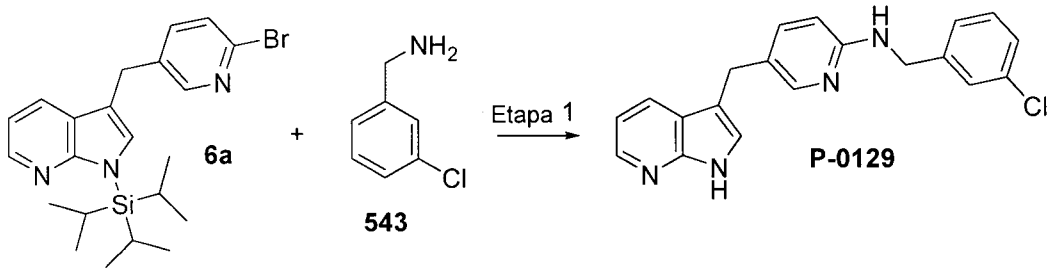


se preparó siguiendo el protocolo del Esquema 168, sustituyendo 4-cloro-benzaldehído **40** con 6-trifluorometil-piridina-3-carbaldehído en la etapa 1 y 1H-Pirrolo[2,3-b]piridina **1** con 5-(1-Metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina (preparada como se describe en el Ejemplo 18, Esquema 172) en la etapa 5. MS (ESI) $[M+H^+]^+$ = 498.0.

Ejemplo 15: Síntesis de (3-cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-0129

[0170] (3-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-0129** se sintetizó en 1 etapa como se muestra en el Esquema 169.

Esquema 169



*Etapa 1 – Preparación de (3-cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0129**):*

[0171] 3-(6-bromo-piridin-3-ilmetil)-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**6a**, 10 mg, 0.023 mmol) se combinó con 3-clorobencilamina (**543**, 13 mg, 0.093 mmol) en dioxano (0.3 ml). Tris(dibencilidenoacetona)-dipaladio(0) (3 mg), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (Xantphos, 3 mg) y *ter*-butóxido de sodio (15 mg) se agregaron. La mezcla se calentó a 100 °C durante la noche. Ácido acético (0.1 ml) se agregó y los solventes se removieron bajo presión reducida. El residuo restante se disolvió en DMSO y se purificó por HPLC de fase inversa en una columna YMC-Pack ODS-A C-18 (50mm x 10mm ID), eluyendo con agua con 0.1 % de ácido trifluoroacético y 5-40% de acetonitrilo con 0.1% de ácido trifluoroacético durante 13 minutos a un flujo volumétrico de 6 ml/minuto para proporcionar el compuesto deseado **P-0129**. MS (ESI) $[M+H^+]^+$ = 349.1.

304

[0172] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 169, reemplazando 3-clorobencilamina **543** con una amina apropiada. Los siguientes compuestos se produjeron siguiendo este procedimiento:

(4-Morfolin-4-ilmetil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0093**),

Piridin-3-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0094**),

(5-Metil-isoxazol-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0095**),

(2-Pirrolidin-1-il-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0096**),

[1-(4-Metanosulfonil-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0097**),

(2-Metoxi-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0098**),

(2-Morfolin-4-il-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0099**),

((R)-1-Fenil-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0125**),

(3-Morfolin-4-il-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0126**),

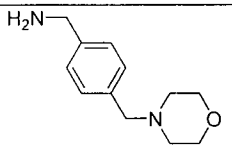
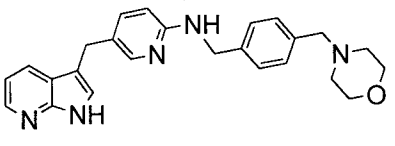
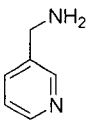
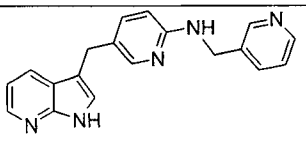
[1-(2-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0127**),

[2-(3-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0128**),

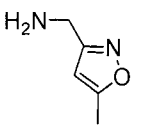
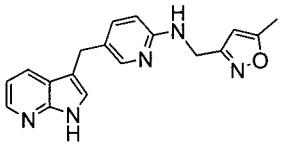
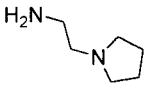
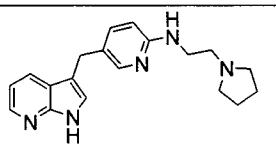
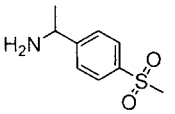
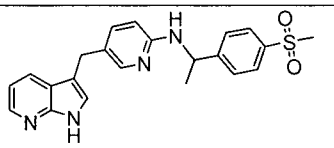
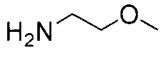
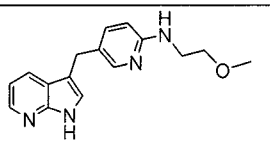
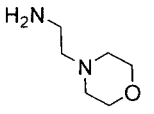
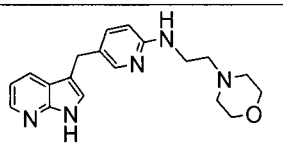
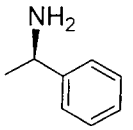
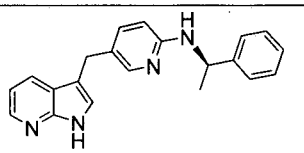
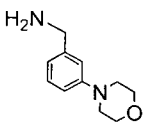
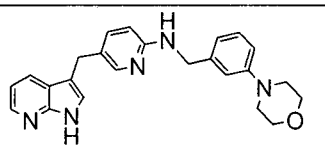
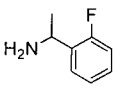
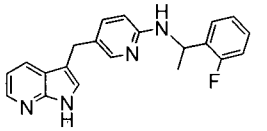
(1-Metil-1H-imidazol-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0130**), y

(1,5-Dimetil-1H-pirazol-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0131**).

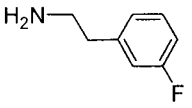
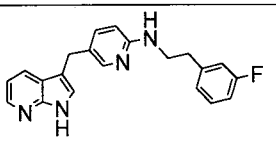
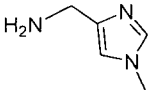
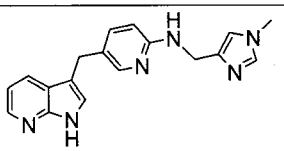
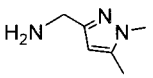
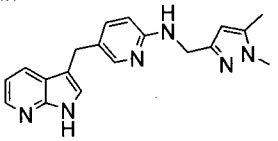
[0173] La siguiente tabla indica la amina (Columna 2) usada en el Esquema 169 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y columna 4 la masa observada.

Número de compuesto	Amina	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0093			414.3
P-0094			316.3

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Número de compuesto	Amina	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0095			319.9
P-0096			322.3
P-0097			407.1
P-0098			283.5
P-0099			338.3
P-0125			329.1
P-0126			400.3
P-0127			347.1

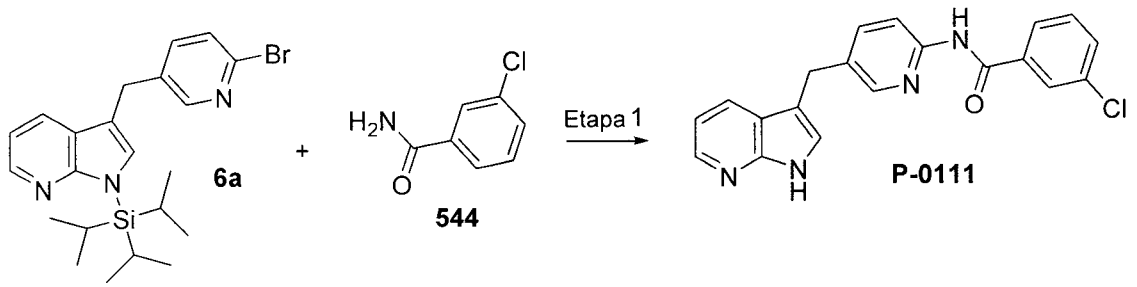
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Número de compuesto	Amina	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0128			347.1
P-0130			319.1
P-0131			333.1

Ejemplo 16: Síntesis de 3-cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida P-0111

[0174] 3-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida **P-0111** se sintetizó en 1 etapa como se muestra en el Esquema 170.

Esquema 170



*Etapa 1 – Preparación de 3-cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0111**):*

[0175] 3-(6-Bromo-piridin-3-ilmetil)-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**6a**, 10 mg, 0.023 mmol) se combinó con 3-cloro-benzamida (**544**, 15 mg, 0.096 mmol) en dioxano (0.4 ml). Tris(dibencilidenoacetona)-dipaladio(0) (3 mg), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (Xantphos, 3 mg), y *ter*-butóxido de sodio (15 mg) se agregaron. Carbonato de cesio (20 mg) se agregó y la

mezcla se calentó a 100 °C durante la noche. Ácido acético (0.1 ml) se agregó y los solventes se removieron bajo presión reducida. El residuo restante se disolvió en DMSO (0.2 ml) y se purificó por HPLC de fase inversa en una columna YMC-Pack ODS-A C-18 (50mm x 10mm ID), eluyendo con agua con 0.1 % de ácido trifluoroacético y 5-40% de acetonitrilo con 0.1% de ácido trifluoroacético durante 13 minutos a un flujo volumétrico de 6 ml/minuto para proporcionar el compuesto deseado **P-0111**. MS (ESI) $[M+H^+]^+ = 363.1$.

[0176] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 170, reemplazando 3-cloro-benzamida **544** con una amida apropiada. Los siguientes compuestos se produjeron siguiendo este procedimiento:

3,4-Dicloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0100**),

2-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0101**),

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido 2,5-Dimetil-2H-pirazol-3-carboxílico (**P-0102**),

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido tiofeno-2-carboxílico (**P-0103**),

2-Metoxi-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida (**P-0104**),

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida (**P-0105**),

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido pirazina-2-carboxílico (**P-0106**),

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido piridina-2-carboxílico (**P-0107**),

6-Metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-nicotinamida (**P-0108**),

4-fluoro-3-metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0109**),

5-Metil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido pirazina-2-carboxílico (**P-0110**),

4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida (**P-0112**),

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometoxi-benzamida (**P-0113**),

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida (**P-0114**),

3-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0115**),

3,4-Difluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0116**),

2-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0117**),

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5-fluoro-2-metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0118**),

2-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0119**),

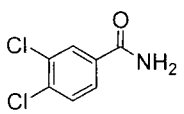
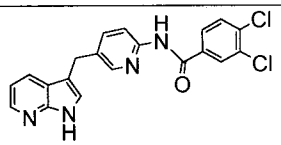
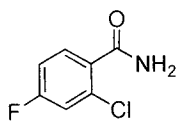
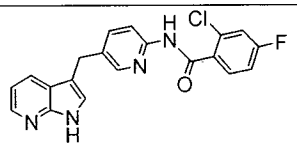
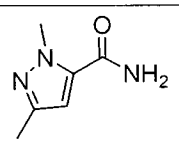
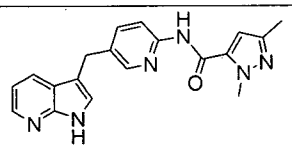
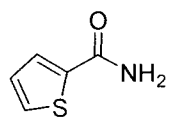
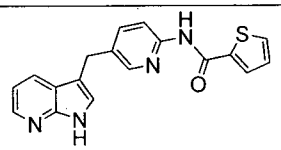
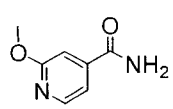
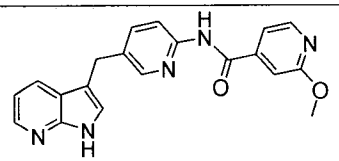
3-Metoxi-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0120**),

3-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0121**),

3-Metil-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida (**P-0122**), y

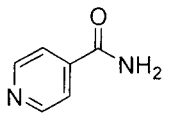
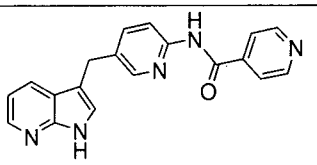
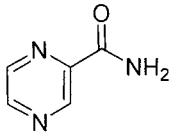
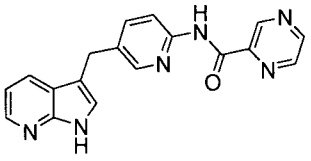
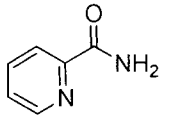
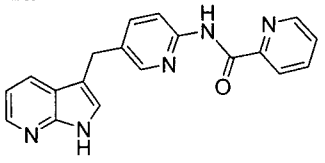
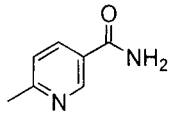
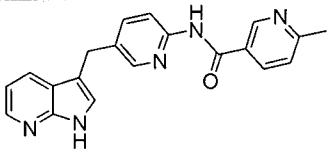
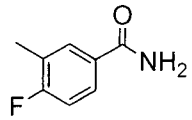
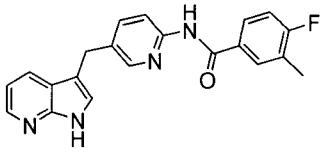
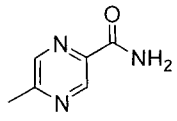
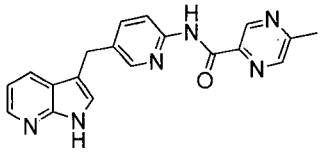
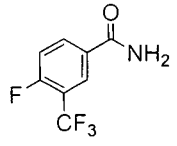
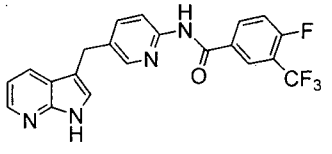
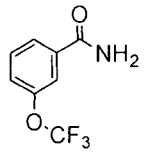
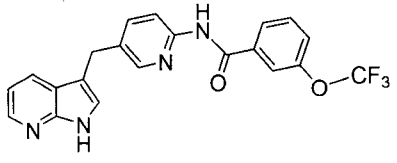
2-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-isonicotinamida (**P-0123**).

[0177] La siguiente tabla indica la amida (Columna 2) usada en el Esquema 170 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 la masa observada.

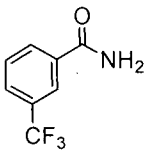
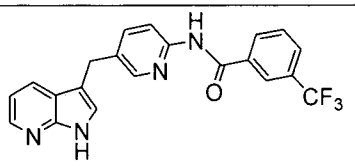
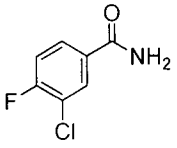
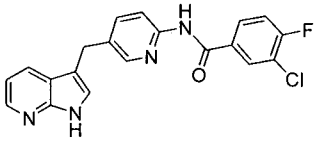
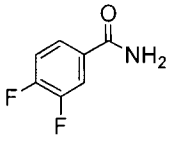
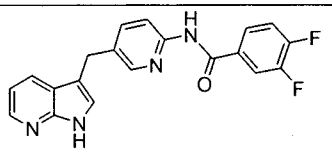
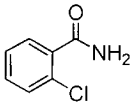
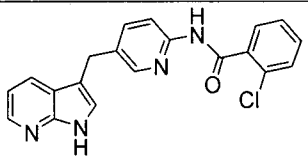
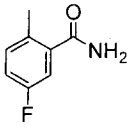
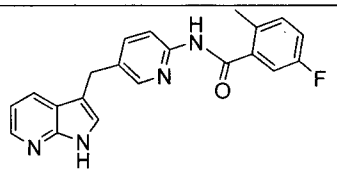
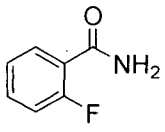
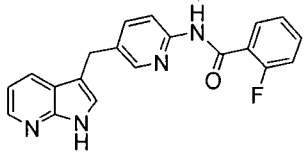
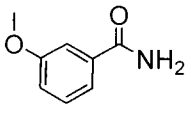
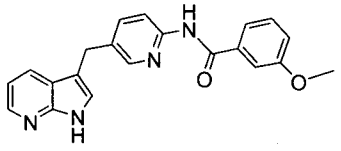
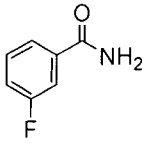
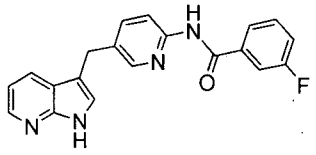
Número de compuesto	Amida	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0100			397.1
P-0101			381.1
P-0102			347.1
P-0103			335.1
P-0104			360.3

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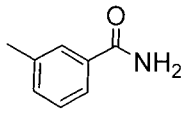
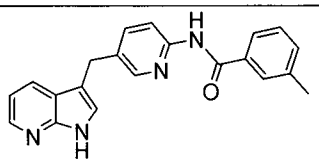
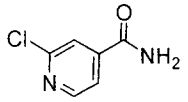
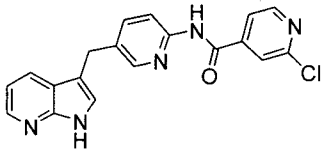
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Número de compuesto	Amida	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0105			329.9
P-0106			331.1
P-0107			329.9
P-0108			344.3
P-0109			361.1
P-0110			345.1
P-0112			415.1
P-0113			413.1

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Número de compuesto	Amida	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0114			397.1
P-0115			381.1
P-0116			365.1
P-0117			363.1
P-0118			361.1
P-0119			347.1
P-0120			359.1
P-0121			347.1

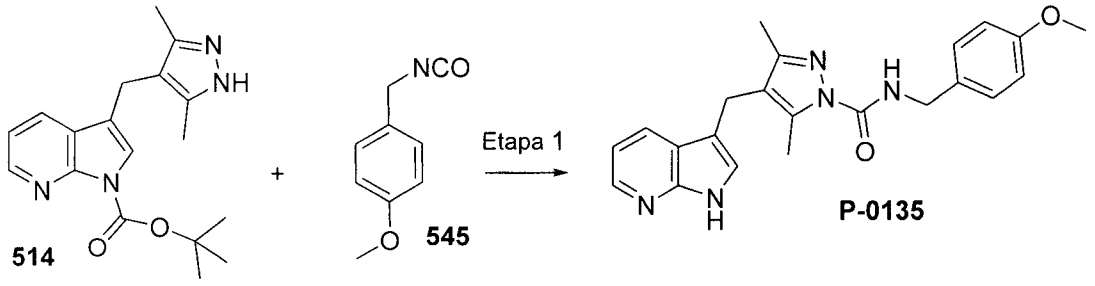
311

Número de compuesto	Amida	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0122			343.1
P-0123			364.3

Ejemplo 17: Síntesis de 4-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico P-0135

[0178] 4-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico **P-0135** se sintetizó en 1 etapa como se muestra en el Esquema 171.

Esquema 171



*Etapa 1 – Preparación de 4-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0135**):*

[0179] ter-butiléster del ácido 3-(3,5-Dimetil-1H-pirazol-4-ilmetil)-pirrolo[2,3-b]piridina-1-carboxílico (**514**, 10 mg, 0.03 mmol) se disolvió en diclorometano (0.5 ml). 1,8-Diazabiciclo[5.4.0]unde-7-eno (6 mg, 0.04 mmol) se agregó. 1-Isocianatometil-4-metoxi-benceno (**545**, 6.5 mg, 0.04 mmol) se agregó. La reacción se dejó proceder a temperatura ambiente durante 30 minutos. Ácido acético (0.2 ml) se agregó a la reacción. Los solventes se removieron bajo presión reducida. El residuo se disolvió en sulfóxido de dimetilo (0.2 ml) y se purificó por HPLC de fase inversa en una columna

Phenomenex (50mm x 10mm ID), eluyendo con agua con 0.1 % de ácido trifluoroacético y 20-100% de acetonitrilo con 0.1% de ácido trifluoroacético durante 16 minutos a un flujo volumétrico de 6 ml/minuto para proporcionar el compuesto deseado **P-0135**. MS (ESI) $[M+H^+]^+$ = 390.3.

[0180] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 171, reemplazando 1-isocianatometil-4-metoxi-benceno **545** con un isocianato o bromuro apropiado. Los siguientes compuestos se produjeron siguiendo este procedimiento:

3-(1-Bencil-3,5-dimetil-1H-pirazol-4-ilmetil)-1H-pirrolo[2,3-b]piridina (**P-0133**),

2-[3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-il]-1-fenil-etanona (**P-0134**),

2-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0136**),

2-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0137**),

3-[3,5-Dimetil-1-(5-trifluorometil-furan-2-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina (**P-0138**),

3-[3,5-Dimetil-1-(5-metil-isoxazol-3-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina (**P-0139**),

4-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0140**),

[2-(4-etoxi-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0141**),

3-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0142**),

3-{3,5-Dimetil-1-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetil]-1H-pirazol-4-ilmetil}-1H-pirrolo[2,3-b]piridina (**P-0143**),

3-[3,5-Dimetil-1-(4-metil-2-fenil-tiazol-5-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina (**P-0144**),

2-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0145**),

[2-(2,4-dicloro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0146**),

[2-(4-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0147**),

[2-(2-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0148**),

((S)-1-fenil-etil)-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0149**),

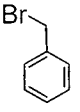
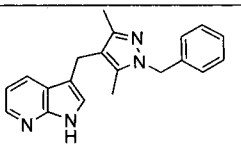
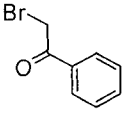
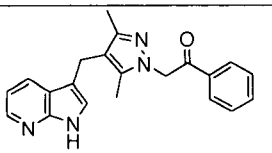
3-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0150**),

4-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0151**),

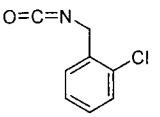
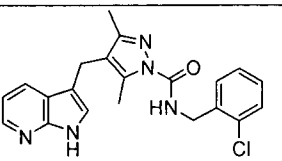
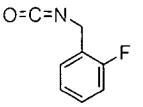
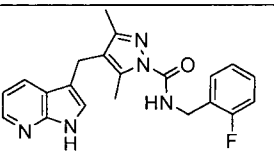
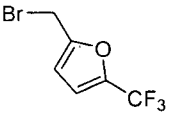
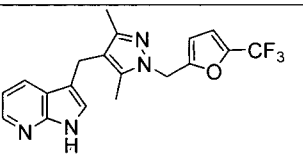
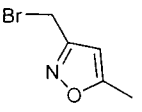
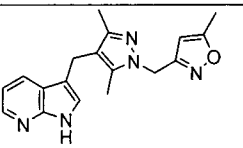
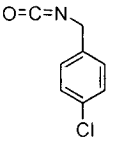
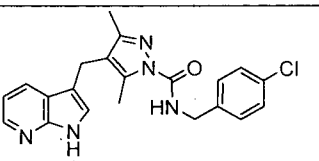
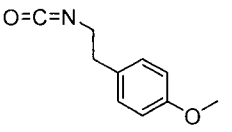
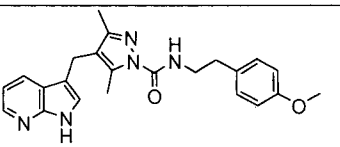
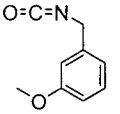
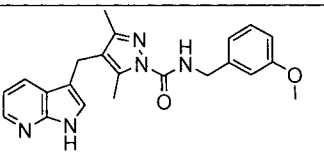
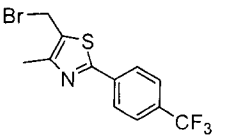
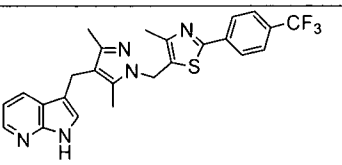
4-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0152**), y

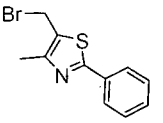
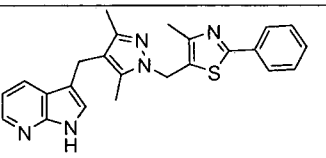
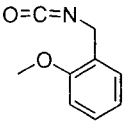
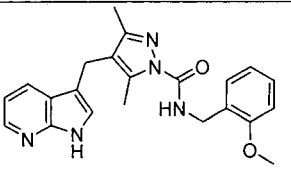
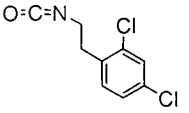
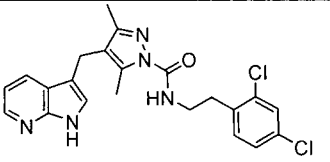
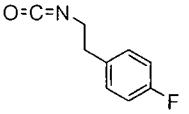
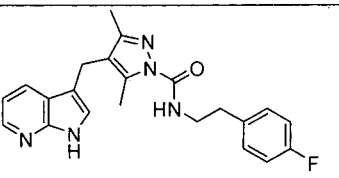
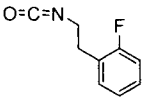
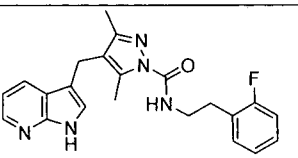
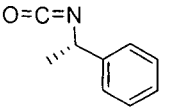
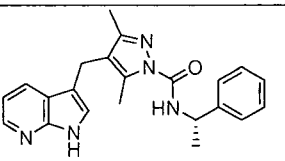
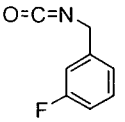
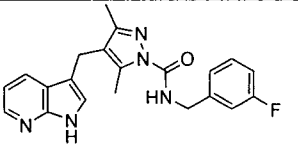
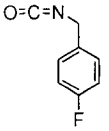
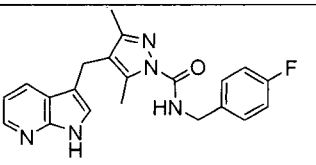
2-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico (**P-0153**).

[0181] La siguiente tabla indica el isocianato o bromuro (Columna 2) usado en el Esquema 171 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 la masa observada.

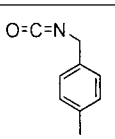
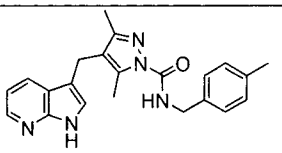
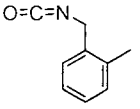
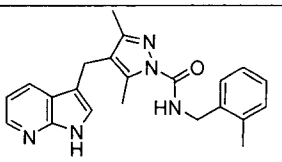
Número de compuesto	Isocianato o bromuro	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0133			317.1
P-0134			345.1

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Número de compuesto	Isocianato o bromuro	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0136			394.3
P-0137			378.3
P-0138			375.1
P-0139			322.3
P-0140			393.9
P-0141			404.3
P-0142			390.3
P-0143			482.3

Número de compuesto	Isocianato o bromuro	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0144			414.3
P-0145			390.3
P-0146			442.3
P-0147			392.3
P-0148			392.3
P-0149			374.3
P-0150			378.3
P-0151			378.3

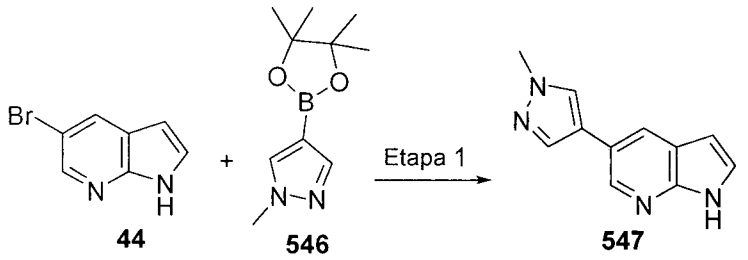
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Número de compuesto	Isocianato o bromuro	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0152			374.3
P-0153			374.3

Ejemplo 18: Síntesis de 5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina 547.

[0182] 5-(1-Metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina **547** se sintetizó en 1 etapa a partir de 5-bromo-1H-pirrolo[2,3-b]piridina **44** como se muestra en el Esquema 172.

Esquema 172



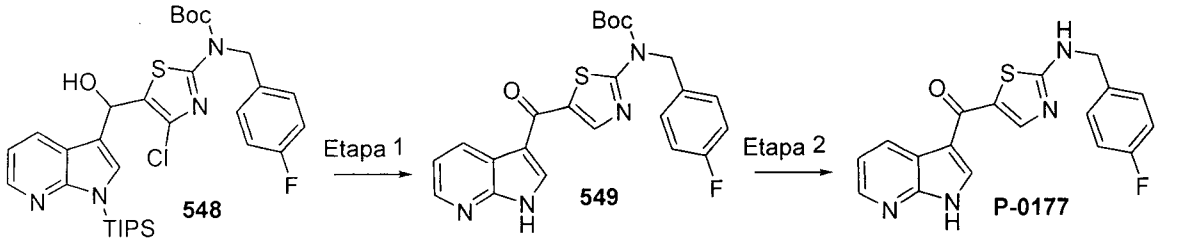
Etapa 1 – Preparación de 5-(1-Metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridina **(547)**:

[0183] A 5-bromo-7-azaindol (**44**, 1.04 g, 5.28 mmol) en 1.00 M de carbonato de potasio en agua (15.8 ml) y tetrahidrofurano (50.0 ml) se agregaron 1-metil-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-1H-pirazol (**546**, 1.65 g, 7.92 mmol), Tetrakis(trifenilfosfina)paladio(0) (0.305 mg, 0.26 mmol) y yoduro de tetra-n-butilamonio (0.20 g, 0.53 mmol). La mezcla de reacción se agitó a 70 °C durante la noche. La mezcla de reacción se vertió en agua y la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, y se concentró. El residuo se purificó con cromatografía de columna en gel de sílice eluyendo con 25% de acetato de etilo en hexano para proporcionar un sólido amarillo claro (**547**, 670 mg, 64.0%). MS(ESI)$[M+H^+]^+$ = 199.4.

Ejemplo 19: Síntesis de [2-(4-fluoro-bencilamino)-tiazol-5-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona P-0177.

[0184] [2-(4-fluoro-bencilamino)-tiazol-5-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **P-0177** se sintetizó en 2 etapas como se muestra en el Esquema 173.

Esquema 173



*Etapa 1 – Preparación de ter-butiléster del ácido (4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridina-3-carbonil)-tiazol-2-il]-carbámico (**549**):*

[0185] Una mezcla de ter-butiléster del ácido {4-cloro-5-[hidroxi-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-tiazol-2-il}-piridin-4-ilmetil-carbámico (**548**, 0.397 g, 0.57 mmol, preparado de acuerdo con el protocolo del Esquema 159, Ejemplo 5, reemplazando 4-(aminometil)piridina **516** con 4-fluoro-bencilamina en la etapa 1, aislada después de la etapa 3), trietilsilano (1.0 ml, 6.3 mmol), y ácido trifluoroacético (0.5 ml, 6 mmol) en acetonitrilo (10 ml) se agitó a 40 °C durante 2 horas. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con bicarbonato de sodio y salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con metanol en diclorometano para proporcionar el compuesto deseado como un sólido amarillo (**549**, 0.11 g, 9%). MS (ESI) $[M\text{-}H^+]^+ = 451.10$.

*Etapa 2 – Preparación de [2-(4-fluoro-bencilamino)-tiazol-5-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona (**P-0177**):*

[0186] A una solución de ter-butiléster del ácido (4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridina-3-carbonil)-tiazol-2-il]-carbámico (**549**, 0.11g, 0.2 mmol) en diclorometano (2 ml) se agregó cloruro de hidrógeno (4 M en 1,4-dioxano, 2 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se vertió en solución fría de bicarbonato de sodio, se extrajo con acetato de etilo, se lavó con salmuera y se secó sobre sulfato de magnesio. Después

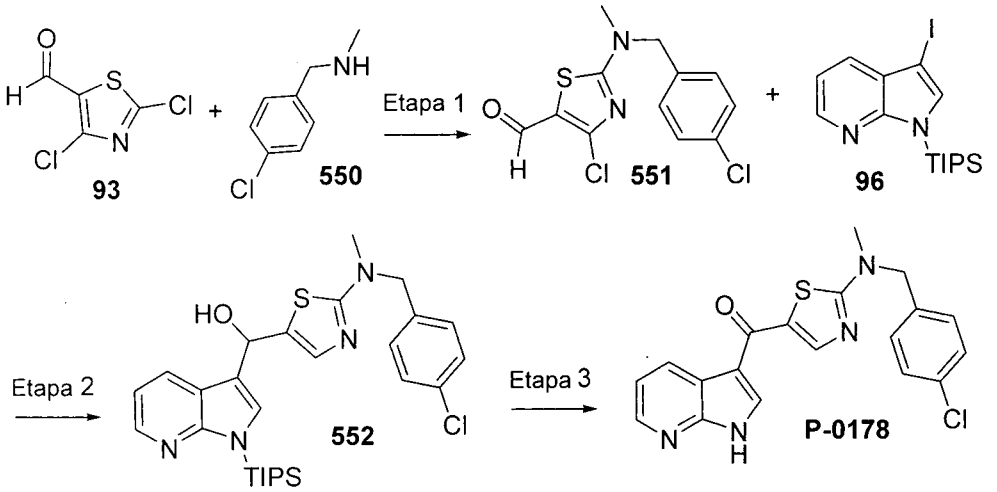
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de la remoción de los solventes, el residuo se lavó con acetato de etilo para proporcionar el compuesto deseado como un sólido amarillo (**P-0177**, 9 mg, 10%). MS (ESI) $[M+H^+]^+ = 353.12$.

Ejemplo 20: Síntesis de {2-[(4-cloro-bencil)-metil-amino]-tiazol-5-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona P-0178.

[0187] {2-[(4-Cloro-bencil)-metil-amino]-tiazol-5-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **P-0178** se sintetizó en 3 etapas como se muestra en el Esquema 174.

Esquema 174



*Etapa 1 – Preparación de 4-cloro-2-[(4-cloro-bencil)-metil-amino]-tiazol-5-carbaldehído (**551**):*

[0188] A una solución de (4-cloro-bencil)-metil-amina (**550**, 2 g, 0.01 mol) y N,N-diisopropiletilamina (4 ml, 0.03 mol) en tetrahidrofurano (50 ml) se agregó 2,4-dicloro-tiazol-5-carbaldehído (**93**, 3 g, 0.01 mmol) en tetrahidrofurano (20 ml) 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, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se recolectó por filtración y se lavó con hexanos para proporcionar el compuesto deseado como un sólido amarillo claro (**551**, 3.6 g, 90%).

*Etapa 2 – Preparación de {4-cloro-2-[(4-cloro-bencil)-metil-amino]-tiazol-5-il}-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**552**):*

[0189] A una solución de 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**96**, 0.82 g, 2.0 mmol) en tetrahidrofurano (5 ml) a -20 °C, cloruro de isopropilmagnesio (2 M en tetrahidrofurano, 1.1 ml, 2.2 mmol) se agregó por goteo. La mezcla de reacción se dejó entibiar a 0 °C en 10 minutos. La

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mezcla de reacción luego se enfrió a -40 °C. A la mezcla de reacción se agregó una solución de 4-cloro-2-[(4-cloro-bencil)-metil-amino]-tiazol-5-carbaldehído (**551**, 0.41 g, 1.4 mmol) en tetrahidrofurano (10 ml). La mezcla de reacción se dejó entibiar a -10 °C en 30 minutos. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con acetato de etilo en hexanos para proporcionar el compuesto deseado como un sólido amarillo (**552**, 0.5 g, 60%). MS (ESI) $[M+H^+]^+$ = 575.29.

*Etapa 3 – Preparación de {2-[(4-cloro-bencil)-metil-amino]-tiazol-5-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona (**P-0178**):*

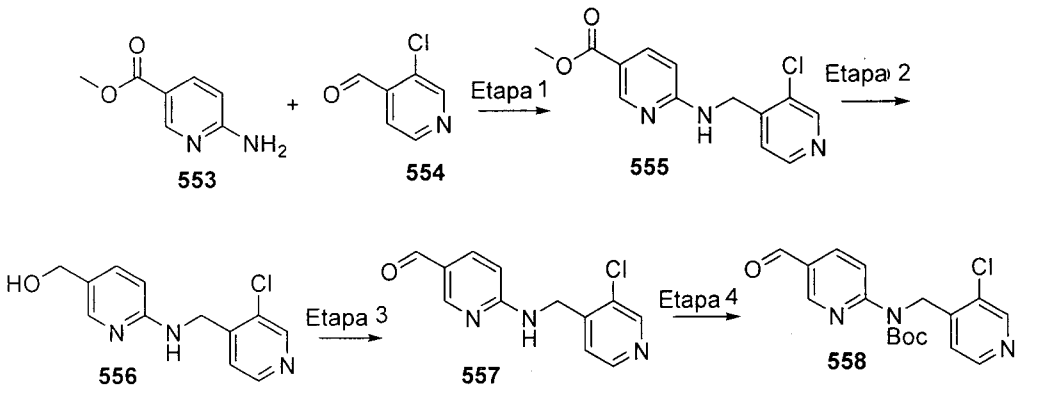
[0190] Una mezcla de {4-cloro-2-[(4-cloro-bencil)-metil-amino]-tiazol-5-il}-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**552**, 1 g, 2 mmol), trietilsilano (2 ml, 12 mmol), y ácido trifluoroacético (1 ml, 13 mmol) en acetonitrilo (10 ml) se agitó a 40 °C durante 2 horas. La mezcla de reacción se vertió en agua helada, se extrajo con acetato de etilo, se lavó con bicarbonato de sodio y salmuera, y se secó sobre sulfato de sodio. Después de la remoción del solvente, el residuo se purificó por cromatografía de columna en gel de sílice eluyendo con metanol en diclorometano para proporcionar el compuesto deseado como un sólido amarillo (**P-0178**, 0.17 g, 30%). MS (ESI) $[M+H^+]^+$ = 383.09.

Ejemplo 21: Síntesis de intermediarios aldehído.

[0191] ter-butiléster del ácido (3-Cloro-piridin-4-ilmetil)-(5-formil-piridin-2-il)-carbámico **558** se sintetizó en 4 etapas a partir de metiléster del ácido 6-amino-nicotínico **553** como se muestra en el Esquema 175.

Esquema 175

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*Etapa 1 – Síntesis de metiléster del ácido 6-[(3-cloro-piridin-4-ilmetil)-amino]-nicotínico (**555**):*

[0192] A metiléster del ácido 6-amino-nicotínico (**553**, 2.15 g, 0.014 mol) en acetonitrilo (60.0 ml) se agregaron 3-cloro-piridina-4-carbaldehído (**554**, 2.00 g, 0.014 mol), trietilsilano (11.00 ml, 0.069 mol) y ácido trifluoroacético (5.00 ml, 0.065 mol). La reacción se agitó a 80 °C durante la noche. La reacción 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 y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**555**, 1.5 g, 38.2%). MS (ESI) $[M+H^+]^+$ = 278.9.

*Etapa 2 – Síntesis de 6-[(3-Cloro-piridin-4-ilmetil)-amino]-piridin-3-il-metanol (**556**):*

[0193] A metiléster del ácido 6-[(3-cloro-piridin-4-ilmetil)-amino]-nicotínico (**555**, 1.00 g, 3.60 mmol) en tetrahidrofurano (120 ml) se agregó una solución de tetrahidroaluminato de litio (1.00 M en tetrahidrofurano, 5.00 ml) bajo una atmósfera de nitrógeno a temperatura ambiente. La reacción se agitó a temperatura ambiente durante la noche, seguido con adición de sulfato de sodio decahidratado. Después de 1 hora, la mezcla de reacción se filtró, concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 2% a 20% de metanol en diclorometano para dar el compuesto deseado como un sólido blanco (**556**, 0.5 g, 56%). MS (ESI) $[M+H^+]^+$ = 250.1.

*Etapa 3 – Síntesis de 6-[(3-cloro-piridin-4-ilmetil)-amino]-piridina-3-carbaldehído (**557**):*

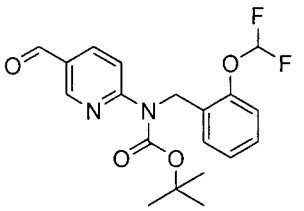
[0194] A 6-[(3-cloro-piridin-4-ilmetil)-amino]-piridin-3-il-metanol (**556**, 0.50 g, 2.00 mmol) en tetrahidrofurano (20.0 ml) se agregó peryodinano de Dess-Martin (1.02 g, 2.40 mmol). La reacción se agitó a temperatura ambiente durante 10 minutos, luego se vertió en carbonato de potasio

acuoso, 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 (**557**, 0.45 g, 91%) que se usó en la siguiente etapa sin purificación posterior.

*Etapa 4 – Síntesis de ter-butiléster del ácido (3-Cloro-piridin-4-ilmetil)-(5-formil-piridin-2-il)-carbámico (**558**):*

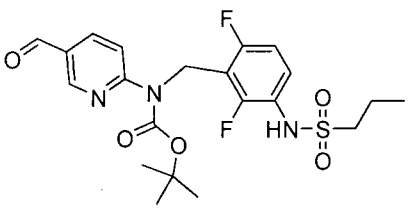
[0195] A 6-[(3-cloro-piridin-4-ilmetil)-amino]-piridina-3-carbaldehído (**557**, 0.45 g, 1.80 mmol) en diclorometano (20.0 ml) se agregaron di-ter-butildicarbonato (0.65 g, 3.00mmol), 4-dimetilaminopiridina (0.012 g, 0.010 mmol) y trietilamina (0.28 ml, 2.00 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**558**, 250 mg, 40.0%).

[0196] ter-butiléster del ácido (2-Difluorometoxi-bencil)-(5-formil-piridin-2-il)-carbámico **559**



se preparó siguiendo el protocolo del Esquema 175, sustituyendo 3-cloro-piridina-4-carbaldehído **554** con 2-difluorometoxi-benzaldehído en la Etapa 1.

[0197] ter-butiléster del ácido [2,6-Difluoro-3-(propano-1-sulfonilamino)-bencil]-(5-formil-piridin-2-il)-carbámico **560**

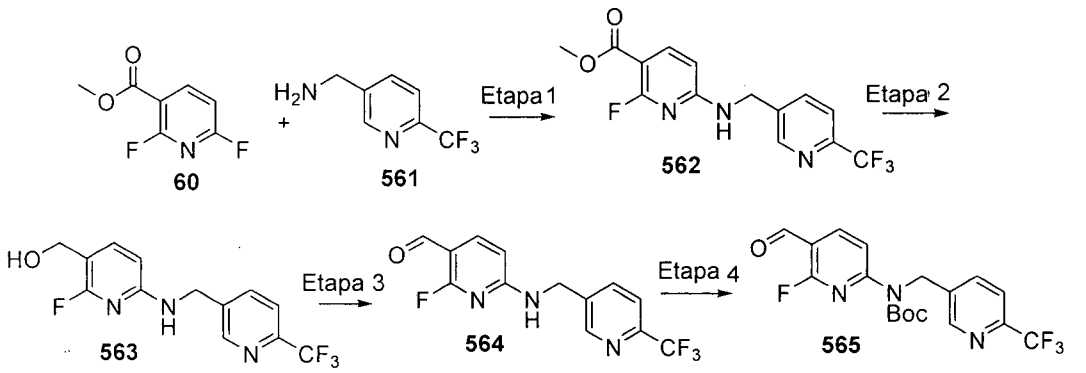


se preparó siguiendo el protocolo del Esquema 175, sustituyendo 3-cloro-piridina-4-carbaldehído **554** con (2,4-difluoro-3-formil-fenil)-amida del ácido propano-1-sulfónico en la Etapa 1. MS (ESI) $[M+H^+]^+ = 470.3$.

[0198] ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-

carbámico **565** se sintetizó en 4 etapas a partir de metiléster del ácido 2,6-Difluoro-nicotínico **60** como se muestra en el Esquema 176.

Esquema 176



*Etapa 1 – Síntesis de metiléster del ácido 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-nicotínico (**562**):*

[0199] A metiléster del ácido 2,6-Difluoro-nicotínico (**60**, 1.82 g, 0.0105 mol) en N,N-dimetilformamida (20.0 ml), bajo una atmósfera de nitrógeno a -40 °C, C-(6-trifluorometil-piridin-3-il)-metilamina (**561**, 1.00 g, 5.68 mmol) se agregó. La reacción se agitó a -40 °C, luego se dejó entibiar a temperatura ambiente durante 2 horas. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 35% a 100% de acetato de etilo en hexano para dar un sólido blanco (**562**, 1.40 g, 74.9). MS (ESI) $[M+H^+]^+$ = 330.1.

*Etapa 2 – Síntesis de 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-il-metanol (**563**):*

[0200] A metiléster del ácido 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-nicotínico (**562**, 1.40 g, 4.25 mmol) en tetrahidrofurano (100.0 ml) bajo una atmósfera de nitrógeno a temperatura ambiente, una solución de tetrahidroaluminato de litio (1.00 M en tetrahidrofurano, 10.0 ml) se agregó lentamente. La reacción se agitó a temperatura ambiente durante la noche, seguido por adición de una cantidad apropiada de sulfato de sodio decahidratado. Después de 1 hora, la mezcla de reacción se filtró y concentró para dar el compuesto sin purificar (**563**, 1.2 g, 93.7%) que se usó en la siguiente etapa sin purificación posterior.

*Etapa 3 – Síntesis de 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridina-3-carbaldehído (**564**):*

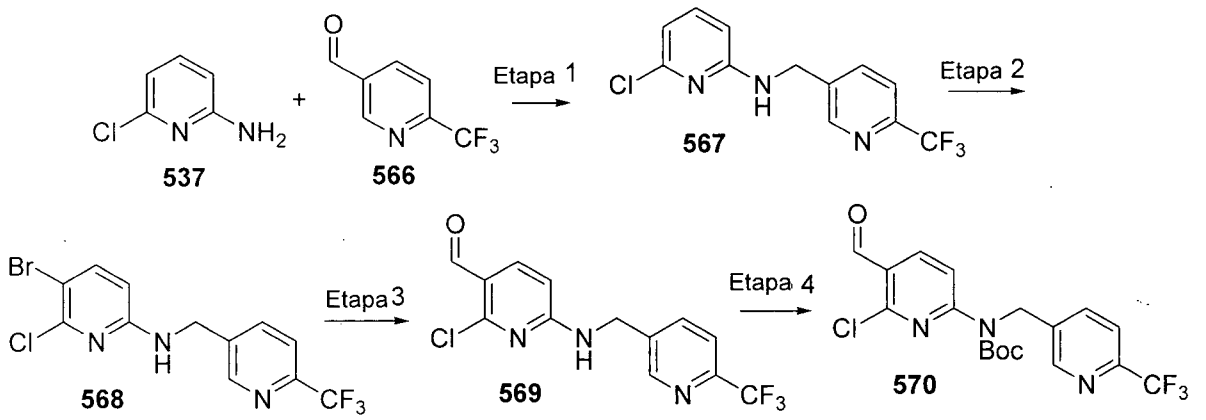
[0201] A 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-il-metanol (**563**, 1.20 g, 3.98 mmol) en diclorometano (40.0 ml) se agregó peryodinano de Dess-Martin (1.86 g, 4.38 mmol). La reacción se agitó a temperatura ambiente durante 10 minutos, luego se vertió en tiosulfato de sodio acuoso y carbonato de potasio, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**564**, 0.28 g, 23.5%).

*Etapa 4 – Síntesis de ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**565**):*

[0202] A 2-fluoro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridina-3-carbaldehído (**564**, 0.28 g, 0.94 mmol) en tetrahidrofurano (10.0 ml) se agregaron di-ter-butildicarbonato (0.245 g, 1.12 mmol) y 4-dimetilaminopiridina (0.050 g, 0.41 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**565**, 0.22 g, 59%).

[0203] ter-butiléster del ácido (6-Cloro-5-formil-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico **570** se sintetizó en 4 etapas a partir de 6-cloro-piridin-2-ilamina **537** como se muestra en el Esquema 177.

Esquema 177



*Etapa 1 – Síntesis de (6-cloro-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-amina (**567**):*

[0204] A 6-cloro-piridin-2-ilamina (**537**, 0.760 g, 5.91 mmol) en acetonitrilo (30.0 ml), 6-

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trifluorometil-piridina-3-carbaldehído (**566**, 1.06 g, 6.05 mmol), ácido trifluoroacético (3.00 ml, 0.0389 mol) y trietilsilano (6.00 ml, 0.0376 mol) se agregaron. La reacción se calentó a reflujo durante 4 horas. La reacción 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, concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**567**, 1.60 g, 94.1%).

*Etapa 2 – Síntesis de (5-bromo-6-cloro-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-amina (**568**):*

[0205] A (6-cloro-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-amina (**567**, 4.50 g, 0.0156 mol) en acetonitrilo (120.0 ml) bajo una atmósfera de nitrógeno, N-bromosuccinimida (3.03 g, 0.0170 mol) en acetonitrilo (50 ml) se agregó lentamente. 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 concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 25% a 100% de acetato de etilo en hexano para dar un sólido blanco (**568**, 6.20 g, 80.2%).

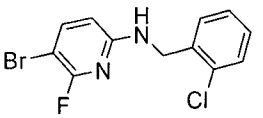
*Etapa 3 – Síntesis de 2-cloro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridina-3-carbaldehído (**569**):*

[0206] A (5-bromo-6-cloro-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-amina (**568**, 4.60 g, 0.0125 mol) en tetrahidrofurano (60.0 ml) bajo una atmósfera de nitrógeno a -78 °C, cloruro de isopropilmagnesio (2.00 M en tetrahidrofurano, 6.44 ml) se agregó durante 10 minutos. La reacción se agitó a -78 °C durante 20 minutos, y luego se dejó entibiar a temperatura ambiente durante 10 minutos. La reacción se enfrió a -78 °C, seguido por la adición de ter-butilitio (1.70 M en hexano, 15.3 ml) durante 10 minutos. Después de 40 minutos, N,N-dimetilformamida (1.23 ml, 0.0158 mol) se agregó y la reacción se agitó a -78 °C durante 40 minutos, luego se dejó entibiar 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 concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 35% a 100% de acetato de etilo en hexano para dar un sólido amarillo claro (**569**, 2.84 g, 71.7%).

*Etapa 4 – Síntesis de ter-butiléster del ácido (6-Cloro-5-formil-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**570**)*

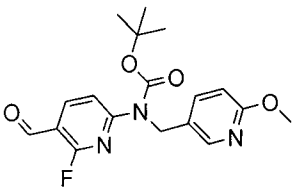
[0207] A una solución de 2-cloro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridina-3-carbaldehído (**569**, 0.545 g, 1.73 mmol) en tetrahidrofurano (10 ml), N,N-diisopropiletilamina (0.60 ml, 3.40 mmol), 4-dimetilaminopiridina (20 mg, 0.10 mmol), y una solución de di-ter-butildicarbonato (0.41 g, 0.0019 mol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se concentró, 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 concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**570**, 0.60 g, 83.6%).

[0208] (5-Bromo-6-fluoro-piridin-2-il)-(2-cloro-bencil)-amina **571**



se preparó siguiendo el protocolo de las Etapas 1 y 2 del Esquema 177, sustituyendo 6-cloro-piridin-2-ilamina **537** y 6-trifluorometil-piridina-3-carbaldehído **566** con 6-fluoro-piridin-2-ilamina y 2-cloro-benzaldehído, respectivamente, en la Etapa 1.

[0209] ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **572**

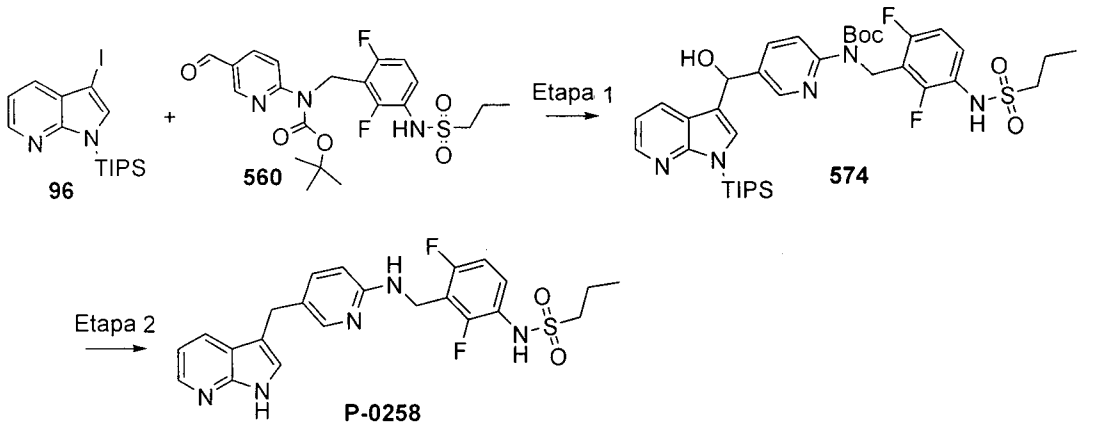


se preparó siguiendo el protocolo del Esquema 177, sustituyendo 6-cloro-piridin-2-ilamina **537** y 6-trifluorometil-piridina-3-carbaldehído **566** con 6-fluoro-piridin-2-ilamina y 6-metoxi-piridina-3-carbaldehído, respectivamente, en la Etapa 1.

Ejemplo 22: Síntesis de (2,4-difluoro-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil-fenil)-amida del ácido propano-1-sulfónico P-0258

[0210] (2,4-difluoro-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil-fenil)-amida del ácido propano-1-sulfónico **P-0258** se sintetizó en 2 etapas a partir de 3-Yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **96** como se muestra en el Esquema 178.

Esquema 178



*Etapa 1 – Síntesis de ter-butiléster del ácido [2,6-difluoro-3-(propano-1-sulfonilamino)-bencil]-5-[hidroxi-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il-carbámico (**574**):*

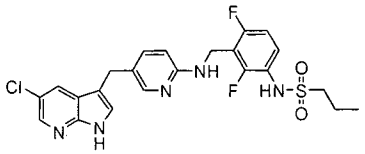
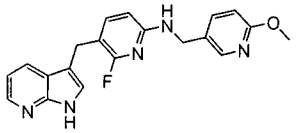
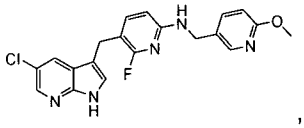
[0211] A una solución de 3-Yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**96**, 0.644 g, 1.61 mmol) en tetrahidrofurano (10.0 ml) a -40 °C bajo nitrógeno, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 0.80 ml) se agregó lentamente. La reacción se dejó entibiar a 15 °C durante 100 minutos, luego se enfrió a -40 °C, seguido por la adición de ter-butiléster del ácido [2,6-Difluoro-3-(propano-1-sulfonilamino)-bencil]-(5-formil-piridin-2-il)-carbámico (**560**, 0.100 g, 0.21 mmol, preparado como se describe en el Ejemplo 21, Esquema 175) en tetrahidrofurano (2.0 ml). La reacción se dejó entibiar a 5 °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 anhidro, y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido amarillo (**574**, 75 mg, 47%). MS (ESI) $[M+H^+]^+$ = 744.7.

*Etapa 2 – Síntesis de (2,4-difluoro-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil-fenil)-amida del ácido propano-1-sulfónico (**P-0258**):*

[0212] A ter-butiléster del ácido [2,6-difluoro-3-(propano-1-sulfonilamino)-bencil]-5-[hidroxi-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metil]-piridin-2-il-carbámico (**574**, 75.0 mg, 0.10 mmol) en acetonitrilo (10.0 ml) se agregaron trietilsilano (0.40 ml, 2.5 mmol) y ácido trifluoroacético (0.20 ml, 2.6 mmol). La reacción se agitó a 80 °C durante 4 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 anhidro, y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice

eluyendo con 2% a 15% de metanol en diclorometano para dar un sólido blanquecino (**P-0258**, 29.3 mg, 61.6%). MS (ESI) $[M+H^+]^+$ = 472.4.

[0213] (3-{[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-2,4-difluoro-fenil)-amida del ácido propano-1-sulfónico (**P-0259**), [6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-0378**), y [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-0379**),

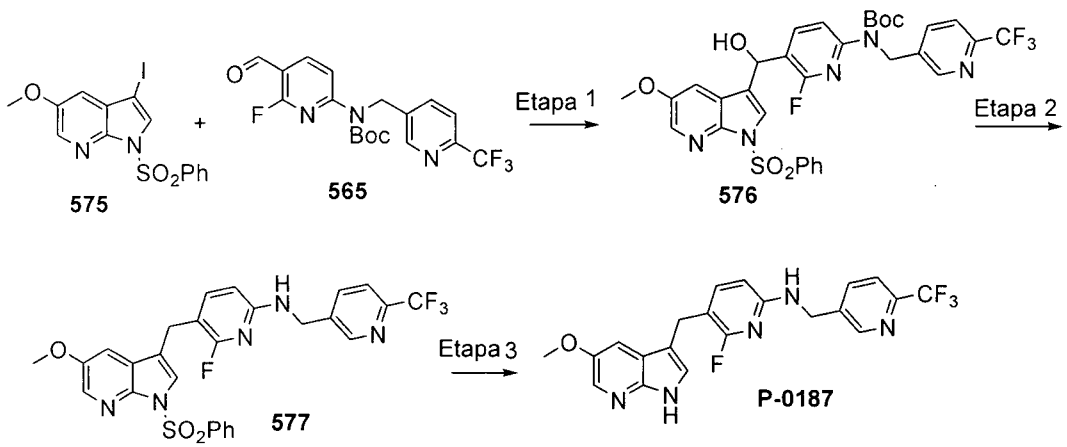

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respectivamente, se prepararon siguiendo el protocolo del Esquema 178. **P-0259** se preparó al reemplazar 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **96** con 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina en la Etapa 1 (MS $[M+H^+]^+$ = 506.1). **P-0378** se preparó al reemplazar ter-butiléster del ácido [2,6-Difluoro-3-(propano-1-sulfonilamino)-bencil]-(5-formil-piridin-2-il)-carbámico **560** con ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico **572** (preparado como se describe en el Ejemplo 21, Esquema 177) en la Etapa 1 (MS $[M+H^+]^+$ = 364.1). **P-0379** se preparó al reemplazar azaindol **96** con 5-cloro-3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina y aldehído **560** con aldehído **572** en la Etapa 1 (MS $[M+H^+]^+$ = 400.0).

Ejemplo 23: Síntesis de [6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina P-0187

[0214] [6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-0187** se sintetizó en 3 etapas a partir de 1-bencensulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina **575** como se muestra en el Esquema 179.

Esquema 179



*Etapa 1 - Síntesis de ter-butiléster del ácido 5-[(1-bencensulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-6-fluoro-piridin-2-il-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**576**):*

[0215] A 1-bencensulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina (**575**, 0.326 g, 0.000788 mol) en tetrahidrofurano (3.00 ml) a -45 °C bajo nitrógeno, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 0.380 ml) se agregó lentamente. La reacción se dejó entibiar a -25 °C en 30 minutos, y luego se enfrió a -45 °C seguido por la adición de ter-butiléster del ácido (6-fluoro-5-formil-piridin-2-il)-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**565**, 80.0 mg, 0.20 mmol, preparado como se describe en el Ejemplo 21, Esquema 176) en tetrahidrofurano (1.0 ml). La reacción se dejó entibiar a temperatura ambiente durante 2 horas. La reacción se vertió en cloruro de amonio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**576**, 0.080 g, 60%). MS (ESI) $[M+H^+]^+$ = 688.1.

*Etapa 2 – Síntesis de [5-(1-Bencensulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**577**):*

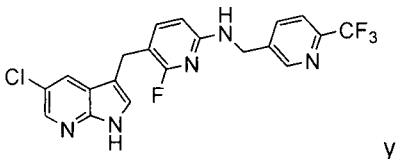
[0216] A ter-butiléster del ácido 5-[(1-bencensulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-6-fluoro-piridin-2-il-(6-trifluorometil-piridin-3-ilmetil)-carbámico (**576**, 0.100 g, 0.15 mmol) en acetonitrilo (12.6 ml) se agregaron trietilsilano (0.34 ml, 2.10 mmol) y ácido trifluoroacético (0.17 ml, 2.20 mmol). La reacción se calentó a 80 °C durante 2 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 anhidro, y se filtró. El filtrado se concentró para dar el compuesto sin purificar (**577**, 90 mg, 100%)

que se usó en la siguiente etapa sin purificación posterior.

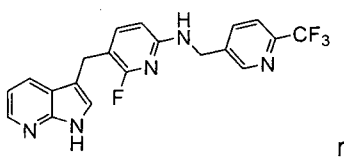
*Etapa 3 – Síntesis de [6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**P-0187**):*

[0217] A [5-(1-bencensulfonil-5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina (**577**, 0.08 g, 0.13 mmol) en tetrahidrofurano (10.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.110 g, 0.35 mmol). 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanquecino (**P-0187**, 8.1 mg, 10%). MS (ESI) $[M+H^+]^+$ = 431.9.

[0218] [6-fluoro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-0186** y [6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina **P-0188**,



y



respectivamente,

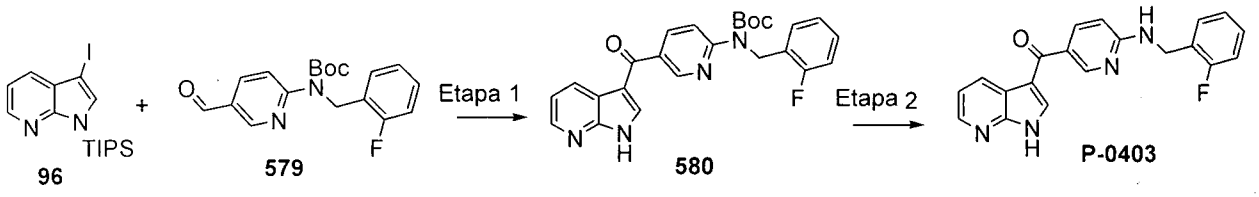
se prepararon siguiendo el protocolo del Esquema 179, sustituyendo 1-bencensulfonil-3-yodo-5-metoxi-1H-pirrolo[2,3-b]piridina **575** con 1-bencensulfonil-3-yodo-5-cloro-1H-pirrolo[2,3-b]piridina o 1-Bencensulfonil-3-yodo-1H-pirrolo[2,3-b]piridina, respectivamente, en la Etapa 1. MS (ESI) $[M+H^+]^+$ = 435.7 y 401.6, respectivamente.

Ejemplo 24: Síntesis de [6-(2-fluoro-bencilamino)-piridin-3-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona P-0403

[0219] [6-(2-fluoro-bencilamino)-piridin-3-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **P-0403** se sintetizó en 2 etapas a partir de 3-Yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **96** como se muestra en el Esquema 180.

Esquema 180

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*Etapa 1 – ter-butiléster del ácido (2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-carbámico (**580**):*

[0220] A 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**96**, 0.550 g, 1.37 mmol) en tetrahidrofurano (15.0 ml) a -40 °C bajo nitrógeno, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 0.65 ml) se agregó lentamente. La reacción se dejó entibiar a 5 °C durante 70 minutos, luego se enfrió a -40 °C, seguido por la adición de ter-butiléster del ácido (2-fluoro-bencil)-(5-formil-piridin-2-il)-carbámico (**579**, preparado de acuerdo con el protocolo del Ejemplo 1, Esquema 19, Etapas 1-3, reemplazando 4-clorobenzaldehído **40** con 2-fluoro-benzaldehído en la Etapa 1) en tetrahidrofurano (4.0 ml). La reacción se dejó entibiar 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**580**, 0.14 g, 26%). MS (ESI) $[M+H^+]^+$ = 447.0.

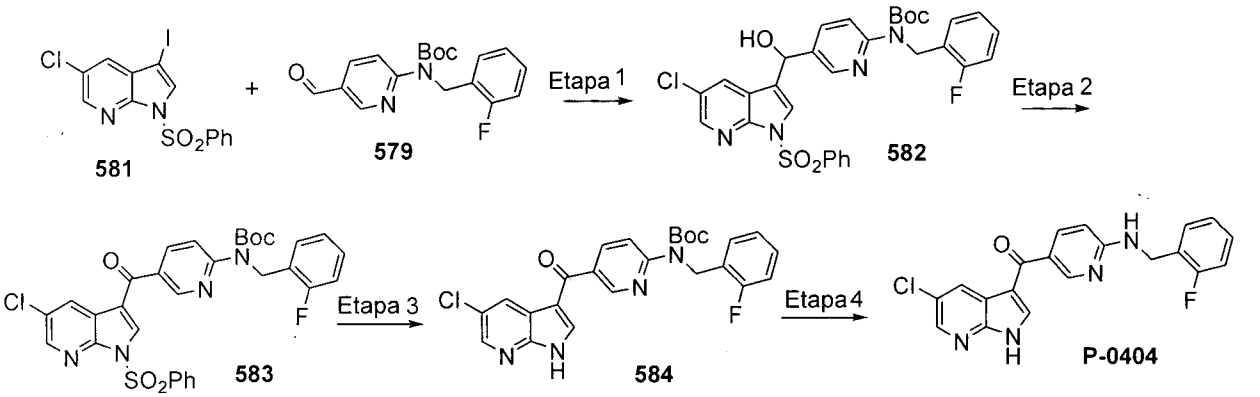
*Etapa 2 - Síntesis de [6-(2-fluoro-bencilamino)-piridin-3-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona (**P-0403**):*

[0221] A ter-butiléster del ácido (2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-carbámico (**580**, 0.080 g, 0.18 mmol) en diclorometano (3.0 ml) se agregó ácido trifluoroacético (1.0 ml, 0.013 mol). La reacción se agitó a temperatura ambiente durante la noche, luego 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 2% a 15 % de metanol en diclorometano para dar el compuesto deseado (**P-0403**, 15.0 mg, 23.0%). MS (ESI) $[M+H^+]^+$ = 347.5.

Ejemplo 25: Síntesis de (5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-[6-(2-fluoro-bencilamino)-piridin-3-il]-metanona P-0404

[0222] (5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-[6-(2-fluoro-bencilamino)-piridin-3-il]-metanona **P-0404** se sintetizó en 4 etapas a partir de 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **581** como se muestra en el Esquema 181.

Esquema 181



*Etapa 1 – Síntesis de ter-butiléster del ácido 5-[(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il-(2-fluoro-bencil)-carbámico (**582**)*

[0223] A una solución de 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**581**, 0.420 g, 1.00 mmol) en tetrahidrofurano (15.0 ml) a -40 °C bajo nitrógeno, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 0.49 ml) se agregó lentamente. La reacción se dejó entibiar a 5 °C durante 70 minutos, luego se enfrió a -40 °C, seguido por la adición de ter-butiléster del ácido (2-fluoro-bencil)-(5-formil-piridin-2-il)-carbámico **579** en tetrahidrofurano (6.0 ml). La reacción se dejó entibiar 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 anhidro, y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**582**, 0.25 g, 41%). MS (ESI) $[M+H^+]^+$ = 623.1.

*Etapa 2 – Síntesis de ter-butiléster del ácido [5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(2-fluoro-bencil)-carbámico (**583**):*

[0224] A ter-butiléster del ácido 5-[(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il-(2-fluoro-bencil)-carbámico (**582**, 0.25 g, 0.40 mmol) en diclorometano (5.0 ml) se agregó peryodinano de Dess-Martin (0.20 g, 0.48 mmol). La reacción se agitó a temperatura

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ambiente durante 10 minutos, luego se vertió en carbonato de potasio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**583**, 0.060 g., 24%).

*Etapa 3 – Síntesis de ter-butiléster del ácido [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(2-fluoro-bencil)-carbámico (**584**):*

[0225] A ter-butiléster del ácido [5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(2-fluoro-bencil)-carbámico (**583**, 60.0 mg, 0.097 mmol) en tetrahidrofurano (1.0 ml) se agregó carbonato de potasio acuoso (1.0 M, 1.0 ml). La reacción se irradió con microondas a 300 watts, 100°C durante 10 minutos, luego 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 (**584**, 0.040 g, 64%) que se usó en la siguiente etapa sin purificación posterior.

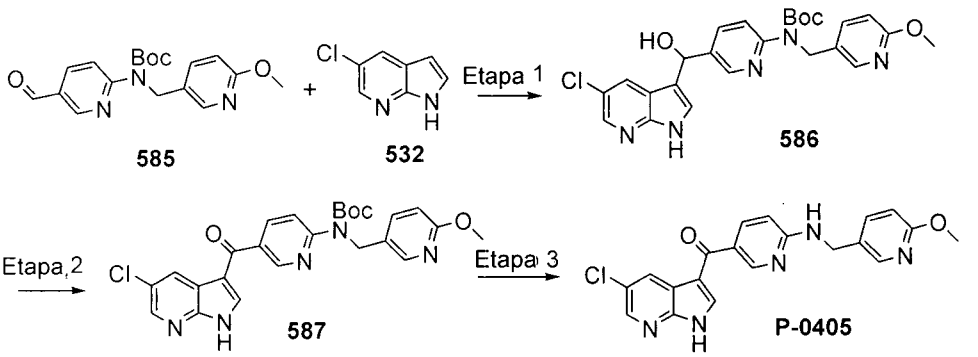
*Etapa 4 – Síntesis de (5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-[6-(2-fluoro-bencilamino)-piridin-3-il]-metanona (**P-0404**):*

[0226] A ter-butiléster del ácido [5-(5-Cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(2-fluoro-bencil)-carbámico (**584**, 0.030 g, 0.062 mmol) en diclorometano (1.0 ml) se agregó ácido trifluoroacético (1.0 ml, 0.013 mol). La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en carbonato de potasio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 2% a 15% de metanol en diclorometano para dar el compuesto deseado (**P-0404**, 2.8 mg, 12%). MS (ESI) $[M+H^+]^+$ = 381.0.

Ejemplo 26: Síntesis de (5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-il-metanona P-0405

[0227] (5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-il-metanona **P-0405** se sintetizó en 3 etapas a partir de 5-Cloro-1H-pirrolo[2,3-b]piridina **532** como se muestra en el Esquema 182.

Esquema 182



*Etapa 1 – Síntesis de ter-butiléster del ácido 5-[(5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il-(6-metoxi-piridin-3-ilmetil)-carbámico (**586**):*

[0228] A 5-cloro-1H-pirrolo[2,3-b]piridina (**532**, 0.092 g, 0.60 mmol) en metanol (15.0 ml) se agregaron ter-butiléster del ácido (5-formil-piridin-2-il)-(6-metoxi-piridin-3-ilmetil)-carbámico (**585**, 0.240 g, 0.70 mmol, preparado de acuerdo con el protocolo del Ejemplo 1, Esquema 19, Etapas 1-3, reemplazando 4-clorobenzaldehído **40** con 6-metoxi-piridina-3-carbaldehído en la Etapa 1) e hidróxido de potasio (1.2 g, 0.021 mol). 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**586**, 0.110 g, 37%).

*Etapa 2 – Síntesis de ter-butiléster del ácido [5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-carbámico (**587**):*

[0229] A ter-butiléster del ácido 5-[(5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-piridin-2-il-(6-metoxi-piridin-3-ilmetil)-carbámico (**586**, 0.060 g, 0.12 mmol) en diclorometano (10.0 ml) se agregó peryodinano de Dess-Martin (0.062 g, 0.15 mmol). La reacción se agitó a temperatura ambiente durante 10 minutos. La reacción se concentró y purificó con una cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**587**, 0.020 g, 33%).

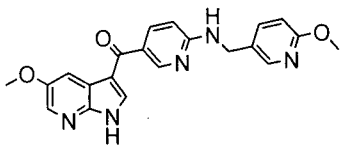
*Etapa 3 – Síntesis de (5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-6-[(6-metoxi-piridin-3-ilmetil)-amino]-piridin-3-il-metanona (**P-0405**):*

[0230] A ter-butiléster del ácido [5-(5-cloro-1H-pirrolo[2,3-b]piridina-3-carbonil)-piridin-2-il]-(6-

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metoxi-piridin-3-ilmetil)-carbámico (**587**, 0.020 g, 0.040 mmol) en diclorometano (2.0 ml) se agregó ácido trifluoroacético (0.30 ml, 0.0039 mol). La reacción se agitó a temperatura ambiente 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**P-0405**, 5.5 mg, 34%). MS (ESI) $[M+H^+]^+$ = 394.3.

[0231] {6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona **P-0406**

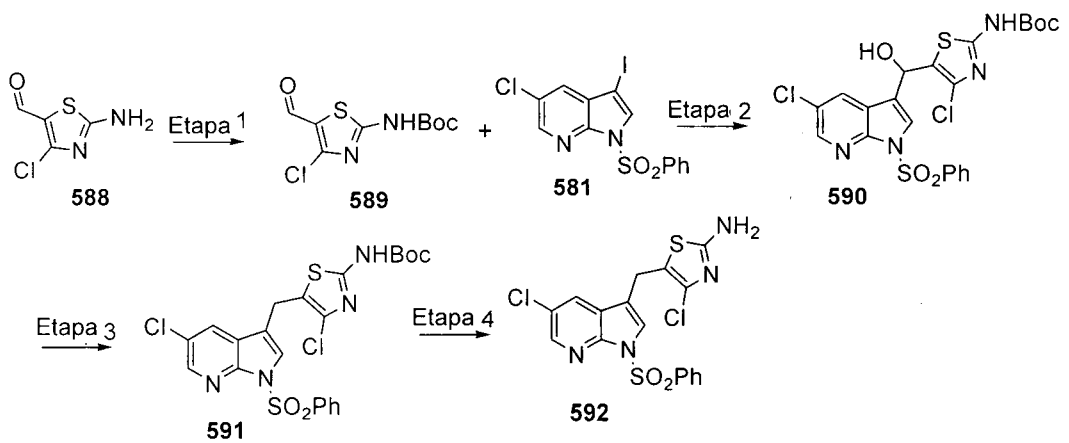


se preparó siguiendo el protocolo del Esquema 182, sustituyendo 5-cloro-1H-pirrolo[2,3-b]piridina **532** con 5-metoxi-1H-pirrolo[2,3-b]piridina en la etapa 1. MS (ESI) $[M+H^+]^+$ = 390.1.

Ejemplo 27: Síntesis del intermediario 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina 592

[0232] 5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **592** se sintetizó en 4 etapas a partir de 2-amino-4-cloro-tiazol-5-carbaldehído **588** como se muestra en el Esquema 183.

Esquema 183



*Etapa 1 – Síntesis de ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**589**):*

[0233] A 2-amino-4-cloro-tiazol-5-carbaldehído (**588**, 5.00 g, 0.0308 mol) en tetrahidrofurano (122

ml) se agregaron di-ter-butildicarbonato (7.38 g, 0.0338 mol) y 4-dimetilaminopiridina (0.35 g, 0.0029 mol). La reacción se agitó a 58 °C durante 2 horas, luego se concentró y purificó con cromatografía de columna en gel de sílice eluyendo con 20% a 80% de acetato de etilo en hexano para dar un sólido amarillo (**589**, 7.0 g, 87%).

*Etapa 2 – Síntesis de ter-butiléster del ácido 5-[(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-4-cloro-tiazol-2-il-carbámico (**590**):*

[0234] A una solución de 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**581**, 4.40 g, 10.5 mmol) en tetrahidrofurano (30.0 ml) a -45 °C bajo nitrógeno, una solución de cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 5.4 ml) se agregó lentamente durante 10 minutos. La reacción se dejó entibiar a -25 °C durante 30 minutos. La reacción se enfrió a -65 °C, seguido por la adición del ter-butiléster desprotonado frío del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico **589**, que se preparó in situ al agregar cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano, 5.0 ml) a ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**589**, 2.51 g, 9.55 mmol) en tetrahidrofurano (23.0 ml) a -78 °C bajo una atmósfera de nitrógeno. La reacción se dejó entibiar a temperatura ambiente en 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 y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 25% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**590**, 3.70 g, 60.3%). MS (ESI) $[M+H^+]^+$ = 554.2.

*Etapa 3 – Síntesis de ter-butiléster del ácido [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-carbámico (**591**):*

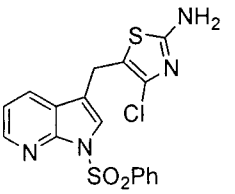
[0235] A ter-butiléster del ácido 5-[(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-4-cloro-tiazol-2-il-carbámico (**590**, 0.200 g, 0.32 mmol) en diclorometano (15.0 ml) se agregaron trietilsilano (0.600 ml, 376 mmol) y ácido trifluoroacético (0.300 ml, 3.89 mmol). La reacción 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 y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 25% a 100% de acetato de etilo en hexano para dar el compuesto

deseado (**591**, 0.155 g, 88.7%). MS (ESI) $[M+H^+]^+$ = 538.9.

*Etapa 4 – Síntesis de 5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina (**592**):*

[0236] A ter-butiléster del ácido [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-carbámico (**591**, 4.30 g, 7.97 mmol) en diclorometano (70.0 ml) se agregó una solución de cloruro de hidrógeno (4.00 M en 1,4-dioxano, 42.0 ml). La reacción se agitó a temperatura ambiente durante 2 días, luego se concentró y tituló con etiléter y acetato de etilo para dar el compuesto deseado (**592**, 2.60 g, 74.2%). MS (ESI) $[M+H^+]^+$ = 439.0.

[0237] 5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **593**

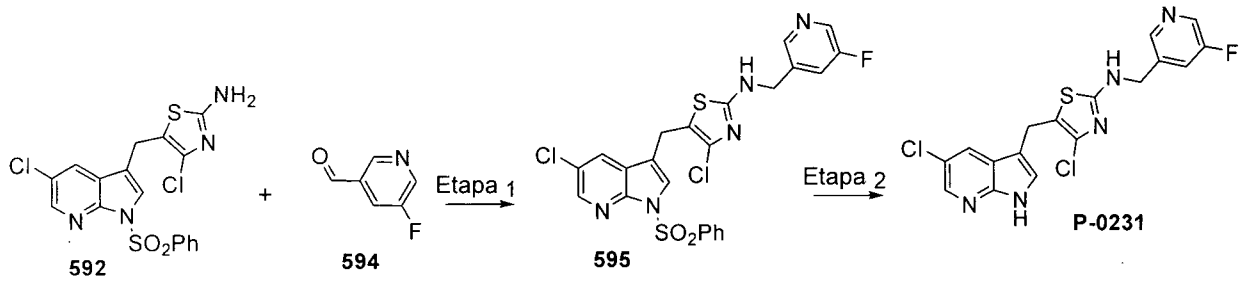


se preparó siguiendo el protocolo del Esquema 183, sustituyendo 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **581** con 1-bencensulfonil-3-yodo-1H-pirrolo[2,3-b]piridina en la Etapa 2. MS (ESI) $[M+H^+]^+$ = 404.4.

Ejemplo 28: Síntesis de [4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina P-0231

[0238] [4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **P-0231** se sintetizó en 2 Etapa etapas a partir de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **592** como se muestra en el Esquema 184.

Esquema 184



592 594 595

Etapa 1 – Síntesis de [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-

*il]-(5-fluoro-piridin-3-ilmetil)-amina (**595**):*

[0239] A 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina (**592**, 50.0 mg, 0.11 mmol, preparada como se describe en el Ejemplo 27, Esquema 183) en etanol (1.60 ml) y ácido acético (0.08 ml) se agregaron 5-fluoro-piridina-3-carbaldehído (**594**, 43 mg, 0.34 mmol) y cianoborohidruro soportado en sílice (1.21 mmol/g, 0.180 g). La reacción se irradió con microondas a 300 watts, 100°C durante 7 minutos. 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% de acetato de etilo en hexano para dar el compuesto deseado (**595**, 0.030 g, 48%).

*Etapa 2 – Síntesis de [4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-0231**):*

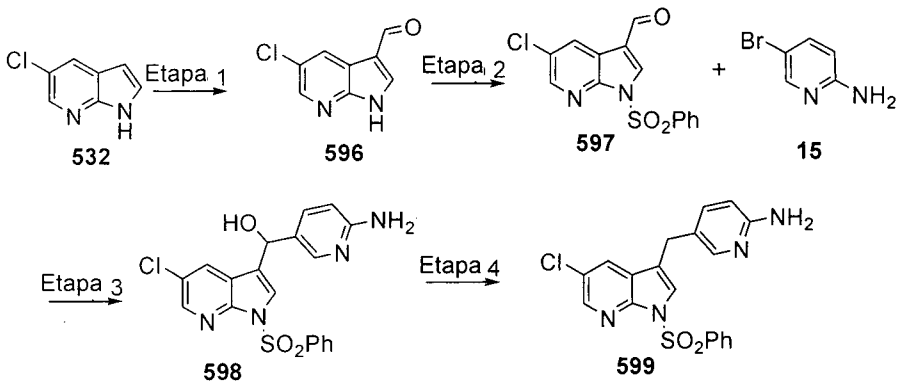
[0240] A [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**595**, 0.030 g, 0.055 mmol) en tetrahidrofurano (6.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.034 g, 0.11 mmol) bajo una atmósfera de nitrógeno. La reacción 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**P-0231**, 1.5 mg, 6.7%). MS (ESI) $[M+H^+]^+$ = 408.1.

Ejemplo 29: Síntesis de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina 599

[0241] 5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **599** se sintetizó en 4 etapas a partir de 5-cloro-1H-pirrolo[2,3-b]piridina **532** como se muestra en el Esquema 185.

Esquema 185

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*Etapa 1 – Síntesis de 5-cloro-1H-pirrolo[2,3-b]piridina-3-carbaldehído (**596**):*

[0242] A 5-cloro-1H-pirrolo[2,3-b]piridina (**532**, 10.0 g, 65.5 mmol) en ácido acético (28.3 ml) se agregaron hexametilenotetramina (11.9 g, 85.2 mmol) y agua (56.7 ml). La reacción se sometió a reflujo durante la noche, seguido por adición de 200 ml de agua. Después de 30 minutos, la reacción se filtró para recuperar el sólido, luego se secó bajo aire para dar el compuesto deseado (**596**, 7.0 g. 59%).

*Etapa 2 – Síntesis de 1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-carbaldehído (**597**):*

[0243] A 5-cloro-1H-pirrolo[2,3-b]piridina-3-carbaldehído (**596**, 3.60 g, 0.0199 mol) en diclorometano (100 ml) se agregaron una solución de hidróxido de potasio (9 M en agua, 50 ml), sulfato ácido de tetrabutilamonio (400 mg, 0.001 mol) y cloruro de bencensulfonilo (2.9 ml, 0.023 mol). 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 anhidro y se filtró. El filtrado se concentró y lavó con acetato de etilo para dar un sólido blanco (**597**, 2.3 g, 36.0%).

*Etapa 3 – Síntesis de (6-amino-piridin-3-il)-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**598**):*

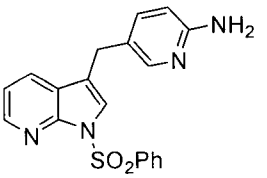
[0244] A 2-amino-5-bromopiridina (**15**, 3.10 g, 17.9 mmol) en tetrahidrofurano (80.0 ml) bajo una atmósfera de nitrógeno a -78 °C, una solución de n-butilitio (2.50 M en hexano, 7.10 ml) se agregó lentamente. Después de 30 minutos, 1,2-bis-(cloro-dimetil-silanil)-etano (3.90 g disuelto en tetrahidrofurano 20.0 ml, 18.1 mmol) se agregó a la mezcla de reacción lentamente, y luego se dejó entibiar a temperatura ambiente durante 1 hora. La reacción se enfrió a -78 °C seguido por la adición de una solución de n-butilitio (2.50 M en Hexano, 7.10 ml). La mezcla de reacción se agitó

a -78 °C durante 30 minutos, luego se dejó entibiar a temperatura ambiente durante 60 minutos. La mezcla de reacción se enfrió a -78 °C, seguido por la adición de una solución de n-butilitio (2.50 M en Hexano, 7.50 ml) lentamente. Después de 60 minutos, 1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridina-3-carbaldehído (**597**, 1.90 g en 30 ml tetrahidrofurano, 5.92 mmol) se agregó a la mezcla de reacción. La mezcla de reacción se agitó a -78 °C durante 2 horas, luego se dejó entibiar a temperatura ambiente durante 1 hora. La reacción 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 2% a 20% de metanol en diclorometano para dar el compuesto deseado (**598**, 1.25 g, 50.9%). MS (ESI) $[M+H^+]^+$ = 415.2.

*Etapa 4 – Síntesis de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**599**):*

[0245] A (6-amino-piridin-3-il)-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**598**, 1.00 g, 0.00241 mol) en diclorometano (25.0 ml) se agregaron trietilsilano (3.00 ml, 0.0188 mol) y ácido trifluoroacético (1.50 ml, 0.0195 mol). La reacción se agitó a temperatura ambiente durante la noche, 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, y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**599**, 0.70 g, 73%).

[0246] 5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **600**



se preparó siguiendo el protocolo del Esquema 185, sustituyendo 5-cloro-1H-pirrolo[2,3-b]piridina **532** con 1H-pirrolo[2,3-b]piridina en la Etapa 1. MS (ESI) $[M+H^+]^+$ = 365.2.

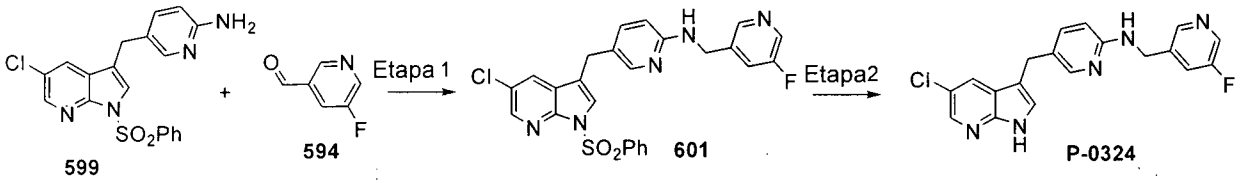
Ejemplo 30: Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina P-0324

[0247] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **P-0324** se sintetizó en 2 etapas a partir de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-

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ilmetil)-piridin-2-ilamina **599** como se muestra en el Esquema 186.

Esquema 186



*Etapa 1 – Síntesis de [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**601**):*

[0248] A 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**599**, 80.0 mg, 0.20 mmol, preparada como se describe en el Ejemplo 29, Esquema 185) en etanol (2.0 ml) y ácido acético (0.10 ml, 0.0018 mol) se agregaron 5-fluoro-piridina-3-carbaldehído (**594**, 62.7 mg, 0.50 mmol) y cianoborohidruro de sodio en gel de sílice (1.200 mmol/g de carga; 0.251 g, 0.30 mmol). La reacción se irradió con microondas a 300 watts, 100 °C durante 10 minutos. 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**601**, 0.060 g, 59%).

*Etapa 2 – Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**P-0324**):*

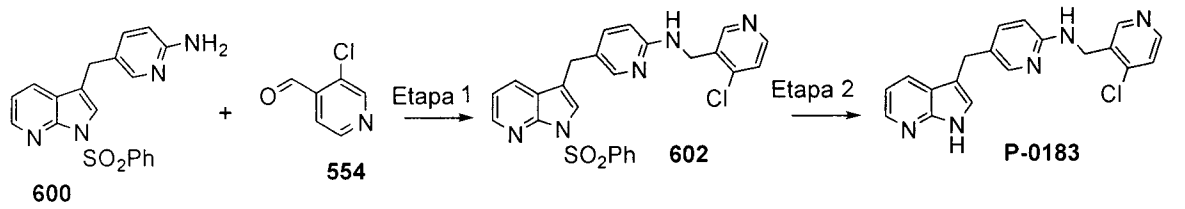
[0249] A [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina (**601**, 0.060 g, 0.12 mmol) en tetrahidrofurano (10.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.11 g, 0.35 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**P-0324**, 13.5mg, 31%). MS (ESI) $[M+H^+]^+$ = 368.0.

Ejemplo 31: Síntesis de (3-Cloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-0183

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[0250] (3-Cloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-0183** se sintetizó en 2 etapas a partir de 5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **600** como se muestra en el Esquema 187.

Esquema 187



*Etapa 1 – Síntesis de [5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-cloro-piridin-3-ilmetil)-amina (**602**):*

[0251] A 5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**600**, 120.0 mg, 0.33 mmol, preparada como se describe en el Ejemplo 29, Esquema 185) en acetonitrilo (10.0 ml) se agregaron 3-cloro-piridina-4-carbaldehído (**554**, 51.3 mg, 0.36 mmol), ácido trifluoroacético (0.30 ml, 0.0039 mol) y trietilsilano (0.60 ml, 0.0038 mol). La reacción se calentó a reflujo durante la noche, luego se vertió en carbonato de potasio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 30% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**602**, 80 mg, 49.6%). MS $[M+H^+]^+$ = 490.2.

*Etapa 2 – Síntesis de (3-cloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0183**):*

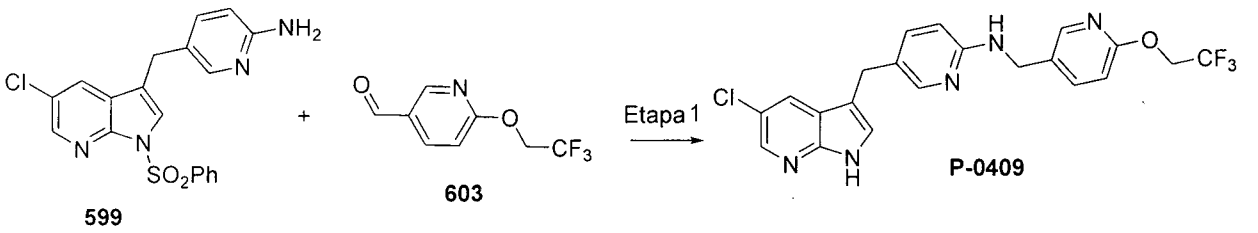
[0252] A [5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(4-cloro-piridin-3-ilmetil)-amina (**602**, 0.08 g, 0.16 mmol) en tetrahidrofurano (10.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.240 g, 0.76 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido amarillo (**P-0183**, 4.0 mg, 7%). MS (ESI) $[M+H^+]^+$ = 350.2.

Ejemplo 32: Síntesis de [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

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[0253] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(5-fluoro-piridin-3-ilmetil)-amina **P-0409** se sintetizó en 2 etapas a partir de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **599** como se muestra en el Esquema 188.

Esquema 188



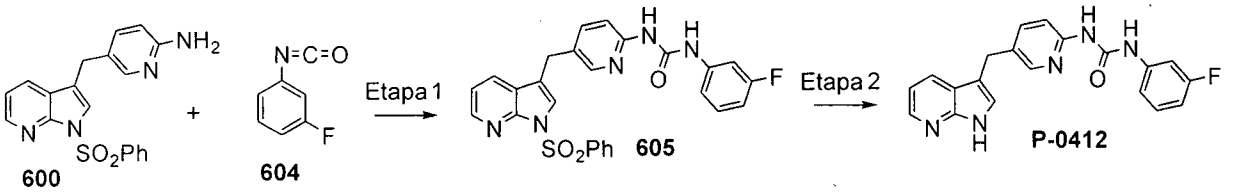
*Etapa 1 – Síntesis de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[6-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina (**P-0409**):*

[0254] A 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**599**, 124.1 mg, 0.31 mmol, preparada como se describe en el Ejemplo 29, Esquema 185) en etanol (3.00 ml) y ácido acético (0.2 ml) se agregaron 6-(2,2,2-trifluoro-etoxi)-piridina-3-carbaldehído (**603**, 164.0 mg, 0.80 mmol) y cianoborohidruro soportado en sílice (1.21 mmol/g, 0.700 g). La reacción se irradió con microondas a 300 watts, 100°C durante 150 minutos. A la reacción se agregó una solución de hidróxido de potasio (9.0 M en agua, 1.0 ml). La reacción se irradió con microondas a 300 watts, 100 °C durante 10 minutos. 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**P-0409**, 10.6 mg, 7.6%). MS ESI) $[M+H^+]^+$ = 448.4.

Ejemplo 33: Síntesis de 1-(3-fluoro-fenil)-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-urea P-0412

[0255] 1-(3-fluoro-fenil)-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-urea **P-0412** se sintetizó en 2 etapas a partir de 5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **600** como se muestra en el Esquema 189.

Esquema 189



*Etapa 1 – Síntesis de 1-[5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-(3-fluoro-fenil)-urea (**605**):*

[0256] A 5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**600**, 150.0 mg, 0.41 mmol, preparada como se describe en el Ejemplo 29, Esquema 185) en acetonitrilo (12.5 ml) se agregaron 3-fluoro-isocianato-benceno (**604**, 61.6 mg, 0.45 mmol), 4-dimetilaminopiridina (10.0 mg, 0.082 mmol) y trietilamina (0.25 ml, 0.0018 mol). La mezcla de reacción se calentó a 70 °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 anhidro, y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**605**, 0.100 g, 48.4%).

*Etapa 2 – Síntesis de 1-(3-fluoro-fenil)-3-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-urea (**P-0412**):*

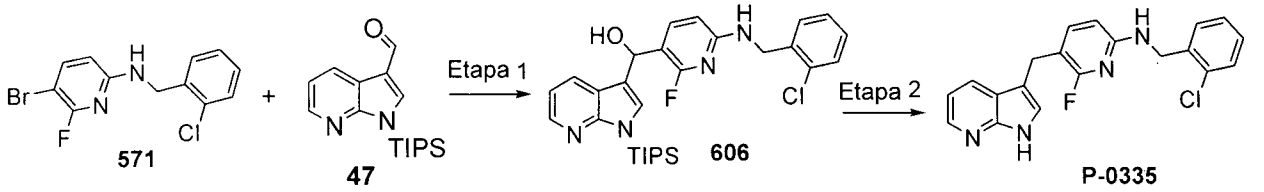
[0257] A 1-[5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-(3-fluoro-fenil)-urea (**605**, 0.100 g, 0.20 mmol) en tetrahidrofurano (10.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.240 g, 0.76 mmol). La reacción se agitó a temperatura ambiente durante 5 horas, luego 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**P-0412**, 17.9 mg, 24.8%). MS (ESI) $[M+H^+]^+$ = 362.2.

Ejemplo 34: Síntesis de (2-cloro-bencil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-0335

[0258] (2-Cloro-bencil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-0335** se sintetizó en 2 etapas a partir de (5-bromo-6-fluoro-piridin-2-il)-(2-cloro-bencil)-amina **571** como se muestra en el Esquema 190.

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Esquema 190



*Etapa 1 – Síntesis de [6-(2-cloro-bencilamino)-2-fluoro-piridin-3-il]-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**606**):*

[0259] A (5-bromo-6-fluoro-piridin-2-il)-(2-cloro-bencil)-amina (**571**, 0.635 g, 2.01 mmol, preparada como se describe en el Ejemplo 21, Esquema 177) en tetrahidrofurano (25.0 ml) bajo una atmósfera de nitrógeno a -78 °C, una solución de n-butilitio (2.50 M en hexano, 0.80 ml) se agregó lentamente. Después de 20 minutos, ter-butilitio (1.7 M en hexano, 2.40 ml) se agregó a la reacción y después de 30 minutos, 1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina-3-carbaldehído (**47**, 0.575 g, 1.90 mmol) en tetrahidrofurano (8.0 ml) se agregó a la reacción. La mezcla de reacción se agitó a -78 °C durante 60 minutos, luego se dejó entibiar a temperatura ambiente durante otros 10 minutos. La mezcla de reacción se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**606**, 0.180 g, 17.6%). MS (ESI) $[M+H^+]^+$ = 539.2.

*Etapa 2 – Síntesis de (2-cloro-bencil)-[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0335**):*

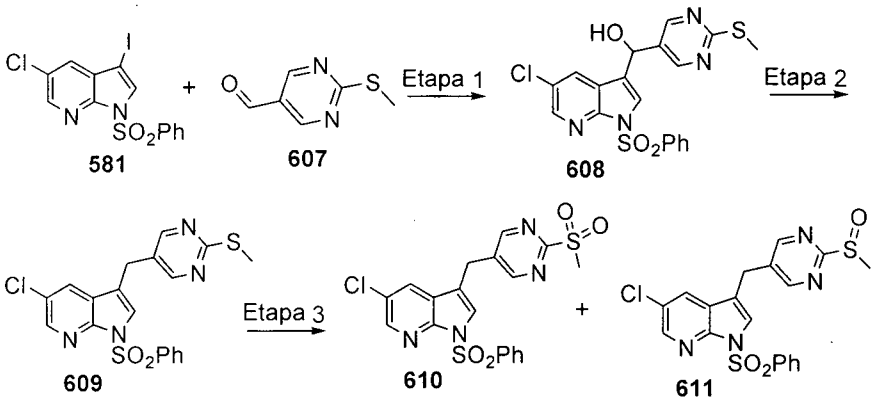
[0260] A [6-(2-cloro-bencilamino)-2-fluoro-piridin-3-il]-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-metanol (**606**, 180.0 mg, 0.33 mmol) en acetonitrilo (15.0 ml) se agregaron trietilsilano (1.00 ml, 6.26 mmol) y ácido trifluoroacético (0.50 ml, 6.50 mmol). La reacción se calentó a reflujo 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 anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**P-0335**, 24.9 mg, 19.4%). MS (ESI) $[M+H^+]^+$ = 367.0.

Ejemplo 35: Síntesis de 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-

pirrolo[2,3-b]piridina 610

[0261] 1-Bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **610** se sintetizó en 3 etapas a partir de 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **581** como se muestra en el Esquema 191.

Esquema 191



*Etapa 1 – Síntesis de (1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**608**):*

[0262] A una solución de 1-Bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina (**581**, 4.36 g, 10.4 mmol) en tetrahidrofurano (100.0 ml) a -40 °C bajo nitrógeno, cloruro de isopropilmagnesio (2.0 M en tetrahidrofurano. 5.06 ml) se agregó lentamente. La reacción se dejó entibiar a 5 °C durante 60 minutos, luego se enfrió a -40 °C, seguido por la adición de 2-metilsulfanil-pirimidina-5-carbaldehído (**607**, 1.30 g, 8.43 mmol, disuelto en tetrahidrofurano 15.0 ml). La reacción se dejó entibiar a 10 °C durante 2 horas. La reacción se vertió en cloruro de amonio acuoso y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 2% a 15% de metanol en diclorometano para dar el compuesto deseado (**608**, 3.00 g, 79.6%). MS (ESI) $[M+H^+]^+$ = 447.2.

*Etapa 2 – Síntesis de 1-bencensulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**609**):*

[0263] A (1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-il)-(2-metilsulfanil-pirimidin-5-il)-metanol (**608**, 0.35 g, 0.78 mmol) en diclorometano (15.0 ml) se agregaron trietilsilano (2.00 ml, 12.52

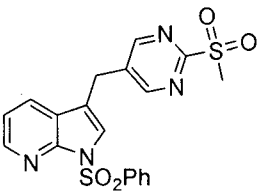
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mmol) y ácido trifluoroacético (1.00 ml, 13.0 mmol). La reacción se agitó a 35 °C durante la noche, luego se concentró, se vertió en carbonato de potasio acuoso, y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**609**, 0.25 g, 74%). MS (ESI) $[M+H^+]^+$ = 430.9.

*Etapa 3 - Síntesis de 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**610**) y 1-bencensulfonil-5-cloro-3-(2-metanosulfinil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**611**):*

[0264] A 1-bencensulfonil-5-cloro-3-(2-metilsulfanil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**609**, 0.500 g, 1.16 mmol) en diclorometano (15.0 ml) se agregó ácido meta-cloroperoxibenzoico (máx. 77%, 0.572 g, 2.55 mmol) a 0 °C. La reacción se agitó a 0 °C durante 70 minutos, luego 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar los compuestos deseados (**610**, 0.310 g, 57.7%), MS (ESI) $[M+H^+]^+$ = 463.1; y (**611**, 0.200 g, 38.6%), MS (ESI) $[M+H^+]^+$ = 447.2.

[0265] 1-Bencensulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **612**



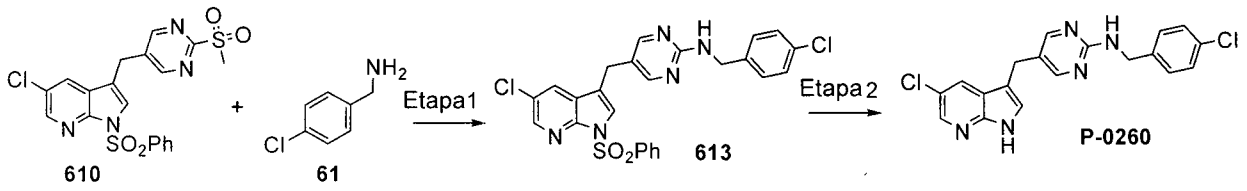
se preparó siguiendo el protocolo del Esquema 191, sustituyendo 1-bencensulfonil-5-cloro-3-yodo-1H-pirrolo[2,3-b]piridina **581** con 1-bencensulfonil-3-yodo-1H-pirrolo[2,3-b]piridina en la Etapa 1.

Ejemplo 36: Síntesis de (4-cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina P-0260

[0266] (4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **P-0260** se sintetizó en 2 etapas a partir de 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **610** como se muestra en el Esquema 192.

Esquema 192

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*Etapa 1 – Síntesis de [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-cloro-bencil)-amina (**613**):*

[0267] A 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**610**, 0.060 g, 0.13 mmol, preparada como se describe en el Ejemplo 35, Esquema 191) en N-metilpirrolidinona (1.80 ml) se agregó p-clorobencilamina (**61**, 0.20 g, 1.4 mmol). La reacción se irradió con microondas a 300 watts, 150 °C durante 15 minutos, luego 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar el compuesto deseado (**613**, 0.05 g, 74%). MS (ESI) $[M+H^+]^+$ = 524.3.

*Etapa 2 – Síntesis de (4-cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0260**):*

[0268] A [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-cloro-bencil)-amina (**613**, 0.050 g, 0.095 mmol) en tetrahidrofurano (10.0 ml) se agregó fluoruro de tetrabutilamonio, trihidratado (0.20 g, 0.63 mmol) bajo una atmósfera de nitrógeno. 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 anhidro y se filtró. El filtrado se concentró y lavó con acetato de etilo en hexano para dar un sólido blanquecino (**P-0260**, 16.9 mg, 46%). MS (ESI) $[M+H^+]^+$ = 385.9.

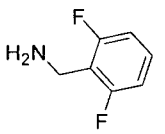
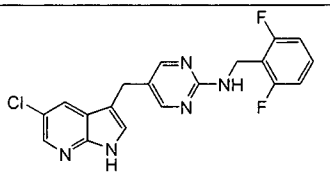
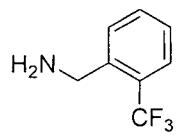
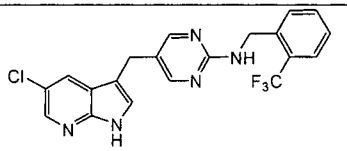
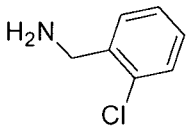
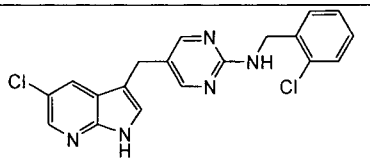
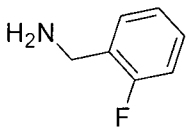
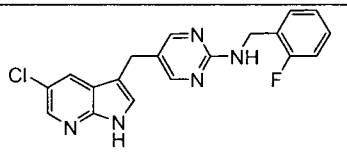
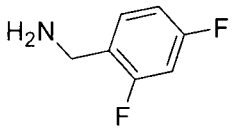
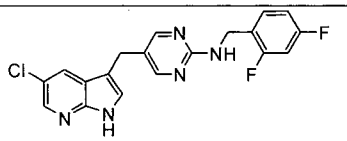
[0269] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 192, sustituyendo p-clorobencilamina **61** con una amina adecuada en la Etapa 1. Los siguientes compuestos se prepararon siguiendo este protocolo:

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,6-difluoro-bencil)-amina (**P-0261**),

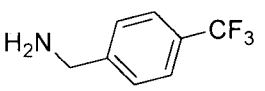
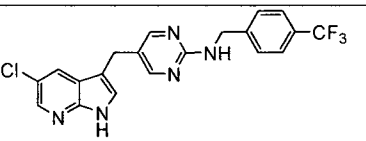
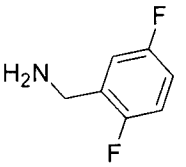
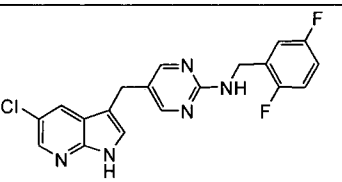
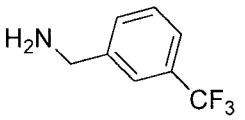
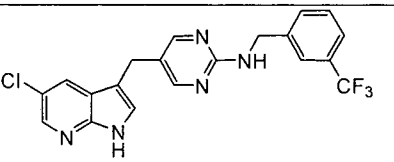
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina (**P-0262**),

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0263**), [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-bencil)-amina (**P-0264**), [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,4-difluoro-bencil)-amina (**P-0265**), [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina (**P-0266**), [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,5-difluoro-bencil)-amina (**P-0267**), y [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometil-bencil)-amina (**P-0268**).

La siguiente tabla indica la amina (Columna 2) usada en el Esquema 192 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 el resultado experimental de la espectrometría de masas.

Número de compuesto	Amina en la Etapa 1	Compuesto	MS (ESI) $[M+H^+]^+$ observada
P-0261			384.1
P-0262			418.9
P-0263			384.2
P-0264			368.2
P-0265			386.2

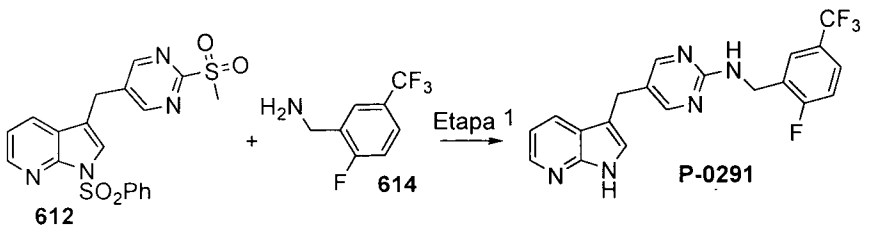
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P-0266			418.9
P-0267			$[M-H^+]^-$ = 384.0
P-0268			419.2

Ejemplo 37: Síntesis de (2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina P-0291

[0270] (2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina **P-0291** se sintetizó en 1 etapa a partir de 1-bencensulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina **612** como se muestra en el Esquema 193.

Esquema 193



*Etapa 1 – Síntesis de (2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0291**):*

[0271] A 1-bencensulfonil-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**612**, 0.080 g, 0.19 mmol, preparada como se describe en el Ejemplo 35, Esquema 191) en N-metilpirrolidinona (1.00 ml) se agregó 2-fluoro-5-trifluorometil-bencilamina (**614**, 0.20 g, 1.0 mmol). La reacción se irradió con microondas a 300 watts, 150°C durante 15 minutos. Hidróxido de potasio en agua (1.00 M, 2.00 ml) se agregó a la reacción. La reacción se irradió con microondas a 300 watts, 90°C durante 10 minutos, luego 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 y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**P-0291**, 37.4 mg, 50%). MS (ESI) $[M+H^+]^+$ = 402.6.

[0272] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 193, sustituyendo 2-fluoro-5-trifluorometil-bencilamina **614** con una amina adecuada. Los siguientes compuestos se prepararon siguiendo este protocolo:

(2,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0292**),

(2-Cloro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0293**),

(3-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0294**),

(3,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0295**),

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0300**),

(2-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0301**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina (**P-0302**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina (**P-0303**),

(5-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0304**),

(2,4-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0305**),

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0306**),

(4-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0307**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina (**P-0308**),

(2-fluoro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0309**),

(2,5-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0310**),

(3-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0311**),

(2-Difluorometoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0312**),

(2,3-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0313**),

(4-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0314**),

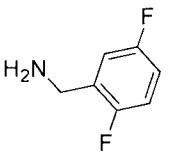
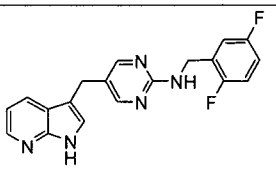
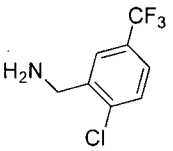
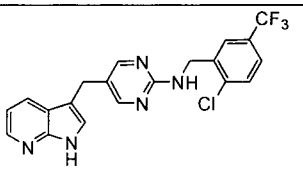
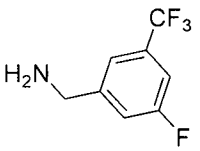
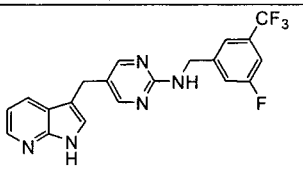
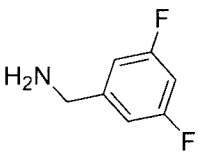
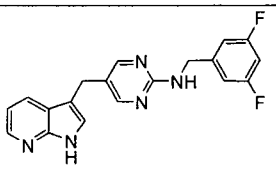
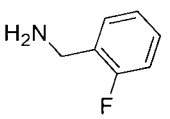
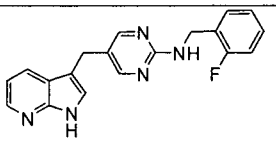
(5-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0315**),

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0316**),

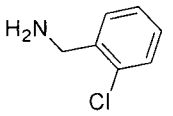
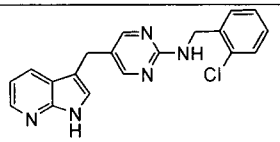
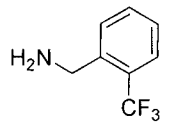
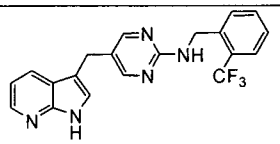
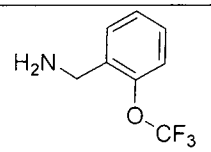
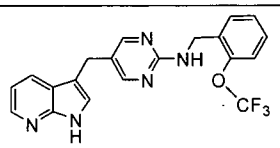
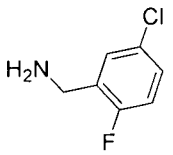
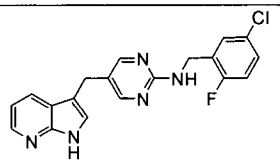
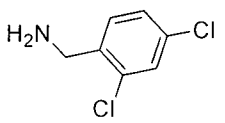
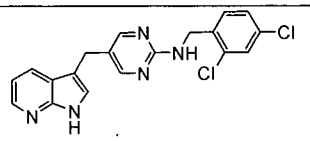
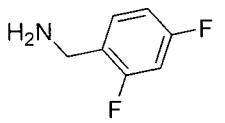
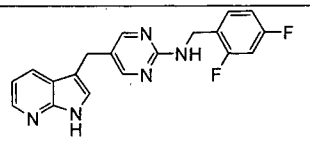
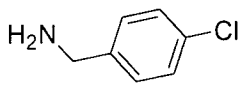
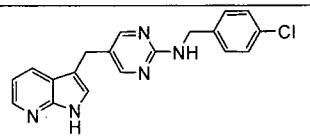
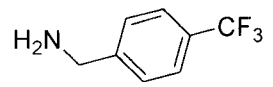
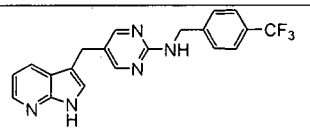
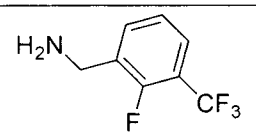
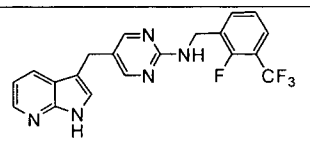
(5-Cloro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0317**),

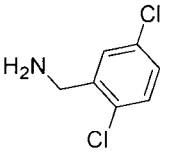
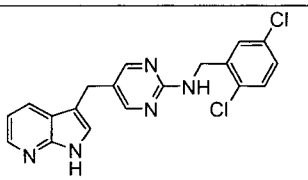
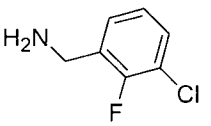
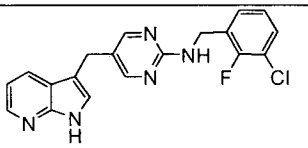
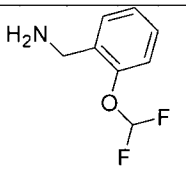
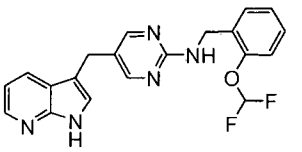
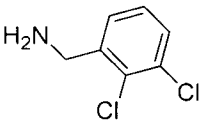
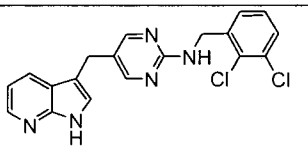
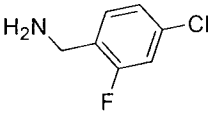
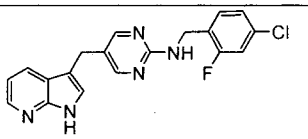
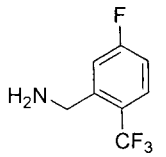
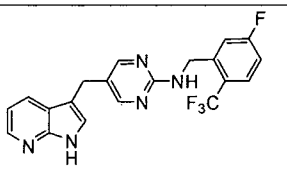
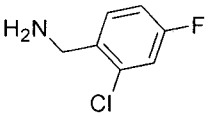
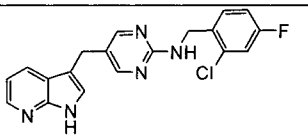
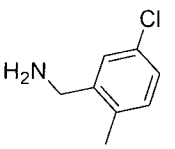
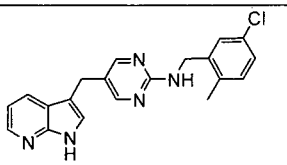
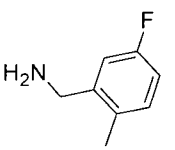
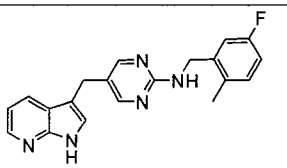
(5-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0318**), (2-fluoro-4-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0319**), (4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0320**), y (2-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0407**).

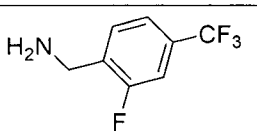
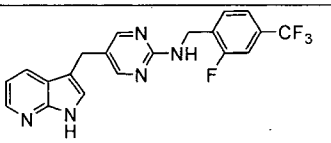
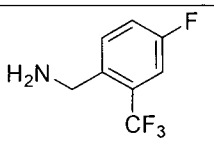
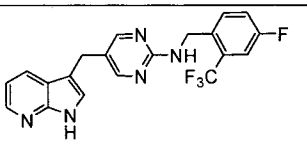
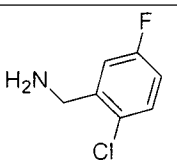
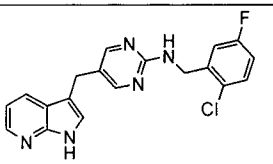
La siguiente tabla indica la amina (Columna 2) usada en el Esquema 193 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 el resultado experimental de la espectrometría de masas.

Número de compuesto	Amina	Compuesto	MS (ESI) $[M+H^+]^+$ observada
P-0292			352.3
P-0293			418.2
P-0294			402.5
P-0295			352.3
P-0300			334.5

352

P-0301			349.9
P-0302			384.0
P-0303			400.5
P-0304			367.9
P-0305			383.9
P-0306			352.4
P-0307			352.0
P-0308			384.0
P-0309			402.5

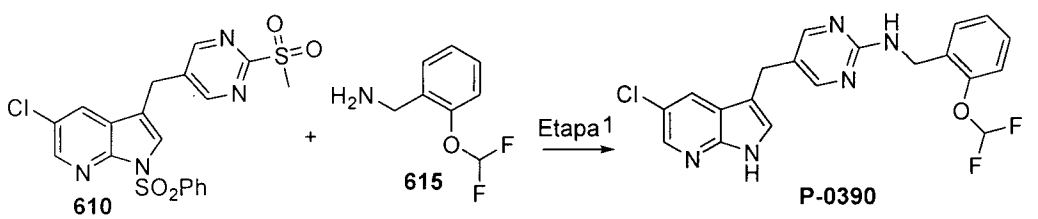
P-0310			389.0
P-0311			368.0
P-0312			382.5
P-0313			385.0
P-0314			367.9
P-0315			402.4
P-0316			368.2
P-0317			364.8
P-0318			348.6

P-0319			402.5
P-0320			402.5
P-0407			368.3

Ejemplo 38: Síntesis de [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-difluorometoxi-bencil)-amina P-0390

[0273] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-difluorometoxi-bencil)-amina **P-0390** se sintetizó en 1 etapa a partir de 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina 610 como se muestra en el Esquema 194.

Esquema 194



Etapa 1 – Síntesis de [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-difluorometoxi-bencil)-amina (P-0390)

[0274] A 1-bencensulfonil-5-cloro-3-(2-metanosulfonil-pirimidin-5-ilmetil)-1H-pirrolo[2,3-b]piridina (**610**, 0.060 g, 0.13 mmol, preparada como se describe en el Ejemplo 35, Esquema 191) en N-metilpirrolidinona (1.40 ml) se agregó 2-difluorometoxi-bencilamina (**615**, 0.200 g, 1.16 mmol). La reacción se irradió con microondas a 300 watts, 150 °C durante 15 minutos. Hidróxido de potasio en agua (1.00 M, 2.00 ml) se agregó a la reacción. La reacción se irradió con microondas a 300 watts, 90 °C durante 10 minutos, luego se vertió en acetato de etilo y agua. La capa orgánica se

concentró y purificó por cromatografía de columna en gel de sílice eluyendo con 20% a 100% de acetato de etilo en hexano para dar un sólido blanco (**P-0390**, 10.9 mg, 20%). MS (ESI) $[M+H^+]^+$ = 418.0.

[0275] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 194, sustituyendo 2-difluorometoxi-bencilamina **615** con una amina adecuada. Los siguientes compuestos se prepararon siguiendo este protocolo:

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-5-trifluorometil-bencil)-amina (**P-0289**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-trifluorometil-bencil)-amina (**P-0391**),

(3-Cloro-2-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0392**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-3-trifluorometil-bencil)-amina (**P-0393**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-4-trifluorometil-bencil)-amina (**P-0394**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,3-difluoro-bencil)-amina (**P-0395**),

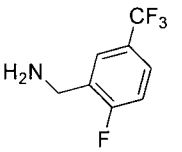
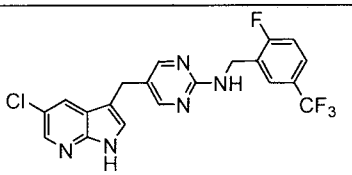
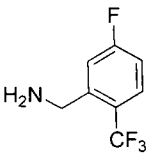
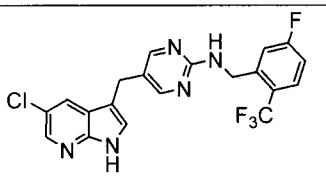
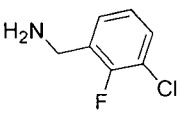
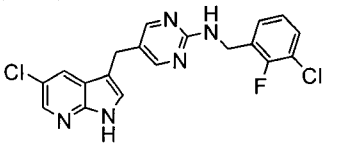
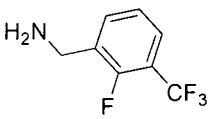
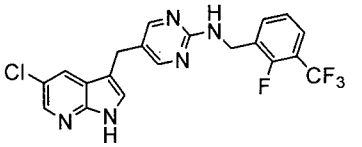
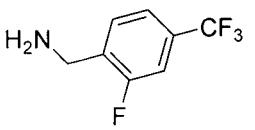
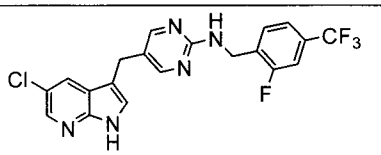
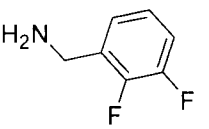
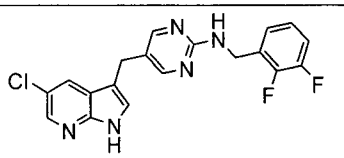
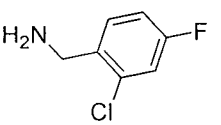
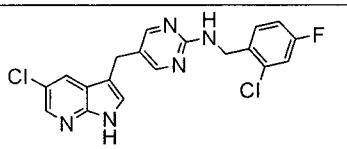
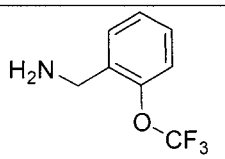
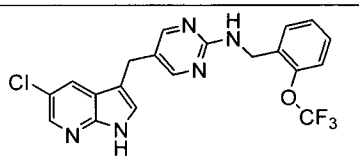
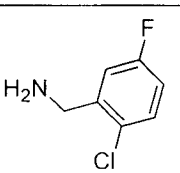
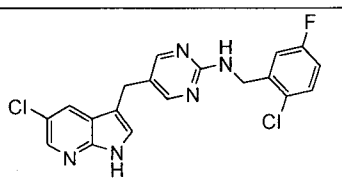
(2-Cloro-4-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0396**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina (**P-0402**), y

(2-Cloro-5-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina (**P-0408**).

La siguiente tabla indica la amina (Columna 2) usada en el Esquema 194 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 el resultado experimental de la espectrometría de masas.

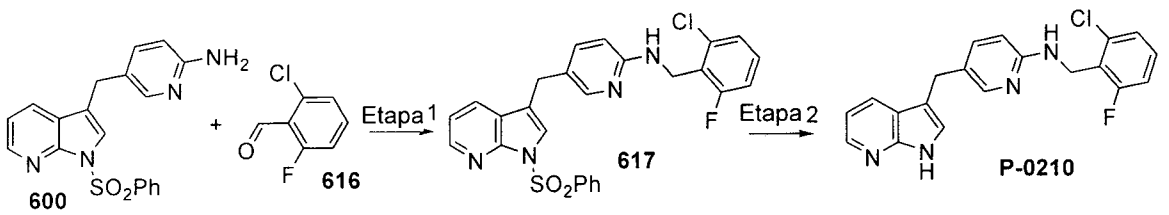
Número de compuesto	Amina	Compuesto	MS (ESI) $[M+H^+]^+$ observada

P-0289			436.0
P-0391			436.0
P-0392			402.0
P-0393			$[M-H^+]^-$ = 434.1
P-0394			437.3
P-0395			386.0
P-0396			402.0
P-0402			434.3
P-0408			402.0

Ejemplo 39: Síntesis de (2-cloro-6-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina P-0210

[0276] (2-Cloro-6-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina **P-0210** se sintetizó en 2 etapas a partir de 5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina **600** como se muestra en el Esquema 195.

Esquema 195



*Etapa 1 – Preparación de [5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-cloro-6-fluoro-bencil)-amina (**617**):*

[0277] 5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamina (**600**, 30 mg, 0.083 mmol, preparada como se describe en el Ejemplo 29, Esquema 185) se combinó con 2-cloro-6-fluoro-benzaldehído (**616**, 26.2 mg, 0.165 mmol) en un vial de reacción para microondas de 2 ml. La mezcla se disolvió en etanol:ácido acético (95:5, 0.6 ml). Cianoborohidruro soportado en sílice (1.0 mmol/g, 83 mg, 0.083 mmol) se agregó y la mezcla se irradió con microondas a 300 watts durante 5 minutos a 100 °C. La sílice se separó por centrifugación y el sobrenadante en solución se decantó. El residuo de sílice se enjuagó con etanol (0.500 ml) y se centrifugó. Los solventes se combinaron y removieron bajo presión reducida para dar el compuesto **617**, que se usó en la siguiente etapa sin purificación posterior.

*Etapá 2 – Preparación de (2-cloro-6-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0210**):*

[0278] [5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-cloro-6-fluoro-bencil)-amina **617** se combinó con metanol:hidróxido de potasio (1M) (1:1, 0.5 ml). La mezcla se calentó a 80 °C durante 2 horas. Ácido acético (0.1 ml) se agregó y los solventes se removieron bajo presión reducida. El residuo restante se disolvió en dimetilsulfóxido (0.4 ml) y se purificó por HPLC de fase

inversa en una columna Phenomenex (50mm x 10mm ID) eluyendo con 0.1 % de ácido trifluoroacético en agua y 20-100 % de acetonitrilo con 0.1% de ácido trifluoroacético durante 16 minutos a un flujo volumétrico de 6 ml/minuto para proporcionar el compuesto deseado **P-0210**. MS (ESI) $[M+H^+]^+ = 367.1$.

[0279] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 195, reemplazando 2-cloro-6-fluoro-benzaldehído **616** con un aldehído apropiado en la Etapa 1. Los siguientes compuestos se produjeron siguiendo este procedimiento:

Fenetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0211**),

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0212**),

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0213**),

(3-Bromo-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0214**),

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0215**),

(2-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0216**),

(2-Metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0217**),

(1-Metil-1H-benzoimidazol-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0218**),

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0219**),

(1H-Benzoimidazol-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0220**),

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0221**),

(5-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0222**),

(3-fluoro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0223**),

(6-Metoxi-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0224**),

(4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0225**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina (**P-0226**),

(3,5-Dicloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0227**),

(6-Morfolin-4-il-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0228**),

(3-fluoro-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0229**),

(5-fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0230**),

(2,4-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0342**),

(3-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0343**),

(2-fluoro-4-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0344**),

(4-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0345**),

(3-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0346**),

(2-Morfolin-4-il-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0347**),

(4-Cloro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0348**),

(2-Cloro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0349**),

(2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0350**),

(2,3-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0351**),

(2-fluoro-3-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0352**),

Dimetil-(5-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-amina (**P-0353**),

(3-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0354**),

(5-fluoro-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0355**),

(3,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0356**),

(2-Propoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0357**),

(2-Morfolin-4-il-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0358**),

(2-Cloro-3-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0359**),

(2-fluoro-6-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0360**),

[2-(2-Morfolin-4-il-etoxi)-bencil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0361**),

(2,3-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0362**),

(2-Cloro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0363**),

(2-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0364**),

(2-fluoro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0365**),

(5-fluoro-2-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0366**),

(2-Difluorometoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0367**),

(2-fluoro-4-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0368**),

[2-(3-Dimetilamino-propoxi)-bencil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0369**),

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(2,6-Dimetoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0370**),

(2-fluoro-5-metoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0371**),

(4-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0372**),

(3-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0373**),

(6-Ciclopentiloxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0374**),

(5-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0375**),

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-[2-(2,2,2-trifluoro-etoxi)-piridin-3-ilmetil]-amina (**P-0376**),

(2-fluoro-3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-fenil)-amida del ácido propano-1-sulfónico (**P-0377**),

(2,5-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0380**),

Pirimidin-5-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0381**),

(5-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0382**),

(2-Etil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0383**),

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**),

Metil-(5-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-pirimidin-2-il)-amina (**P-0386**),

(2-Cloro-4-metanosulfonil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0387**),

(5-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0397**),

(2,2-Difluoro-benzo[1,3]dioxol-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0398**),

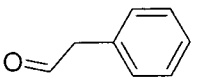
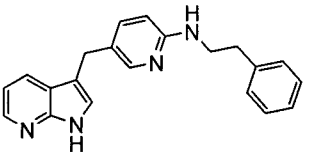
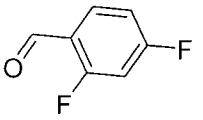
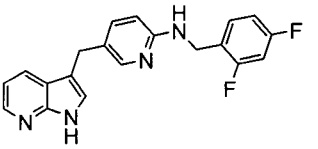
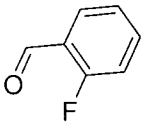
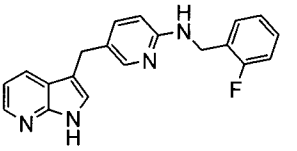
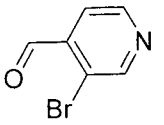
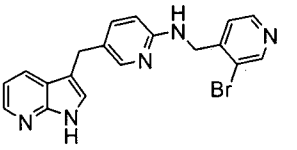
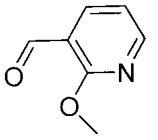
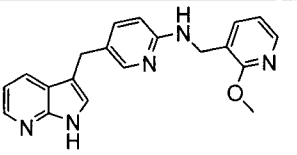
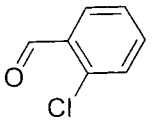
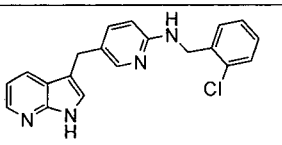
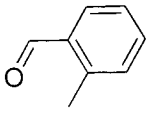
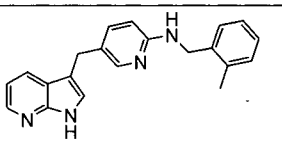
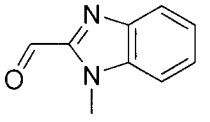
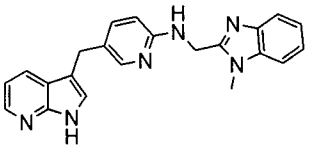
Dimetil-(3-{[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-ilamino]-metil}-piridin-2-il)-amina (**P-0399**),

(5-Cloro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0400**), y

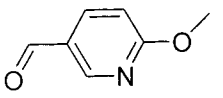
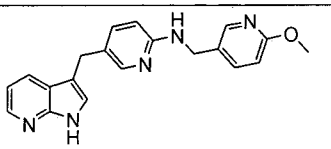
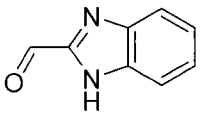
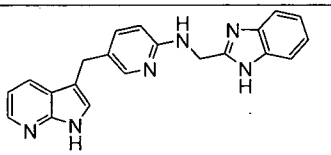
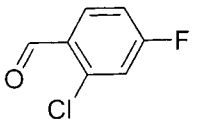
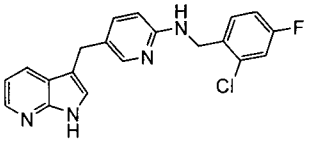
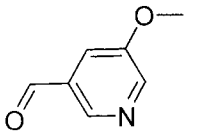
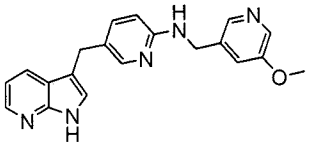
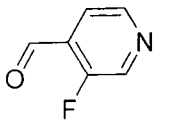
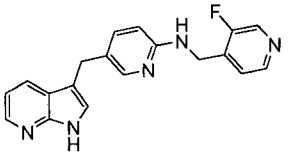
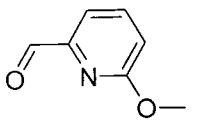
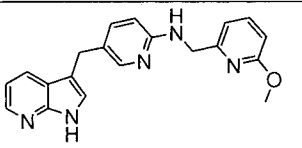
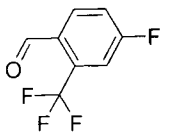
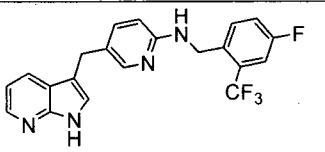
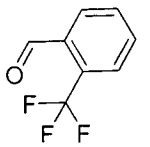
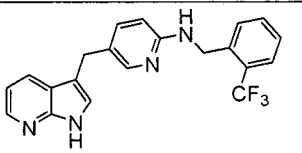
(2-Metoxi-pirimidin-5-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina (**P-0401**).

La siguiente tabla indica el aldehído (Columna 2) usado en la Etapa 1 del Esquema 195 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la Columna 4 el resultado experimental de la espectrometría de masas.

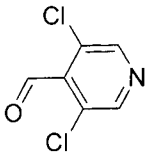
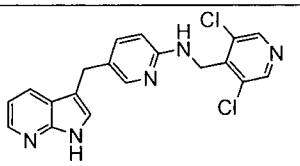
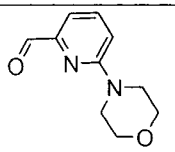
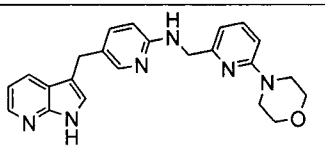
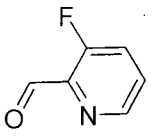
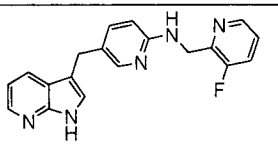
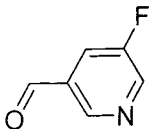
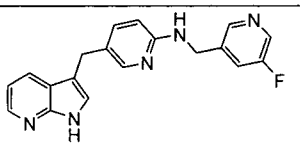
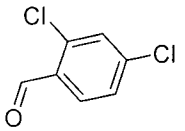
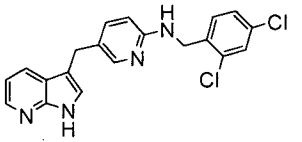
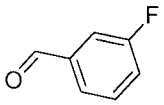
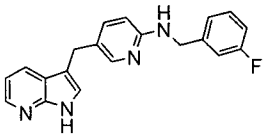
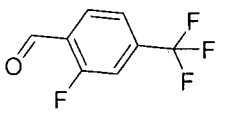
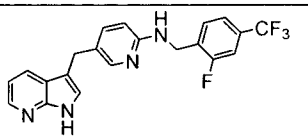
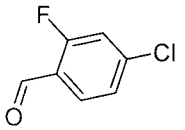
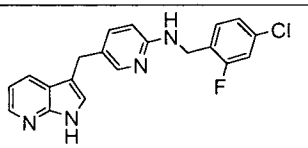
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0211			329.1
P-0212			351.1
P-0213			338.1
P-0214			395.9
P-0215			345.9
P-0216			349.1
P-0217			329.1
P-0218			369.1

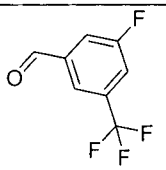
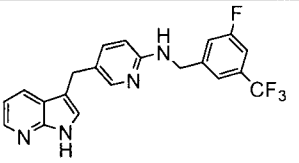
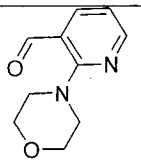
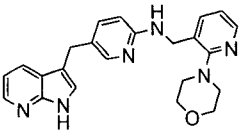
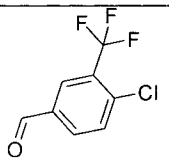
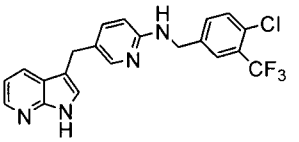
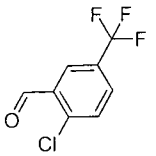
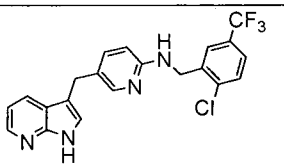
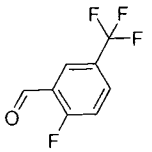
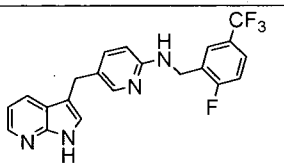
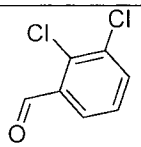
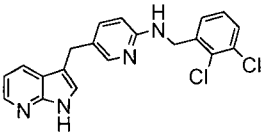
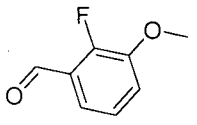
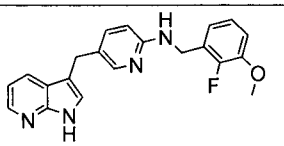
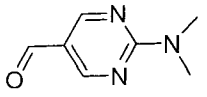
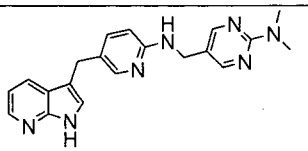
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0219			345.9
P-0220			355.1
P-0221			367.1
P-0222			345.9
P-0223			334.3
P-0224			345.9
P-0225			401.1
P-0226			383.1

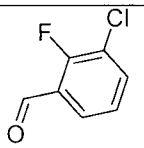
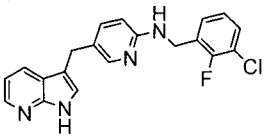
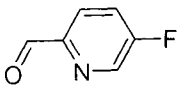
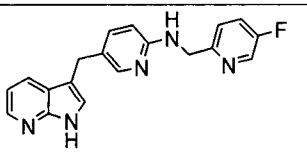
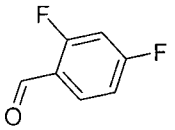
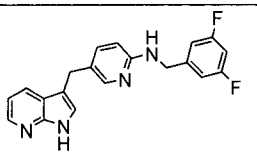
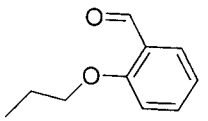
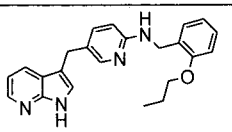
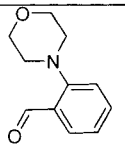
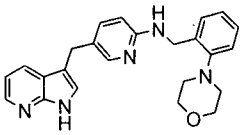
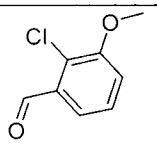
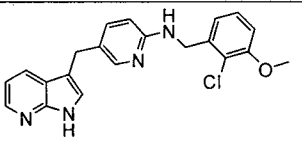
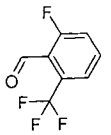
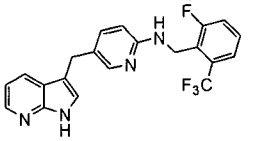
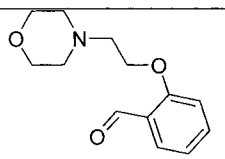
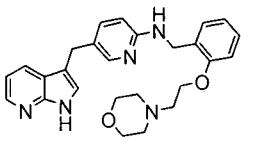
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0227			383.9
P-0228			401.1
P-0229			334.3
P-0230			334.3
P-0342			383.1
P-0343			333.1
P-0344			401.1
P-0345			367.1

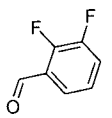
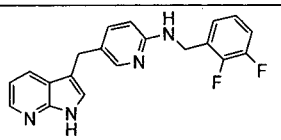
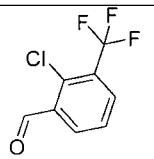
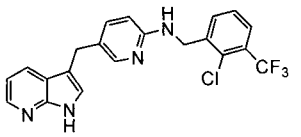
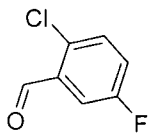
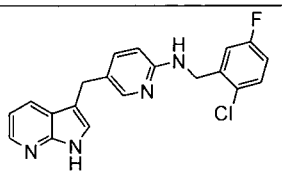
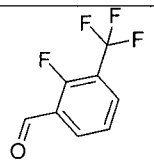
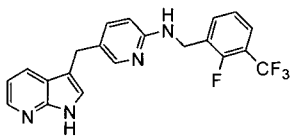
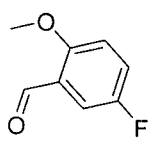
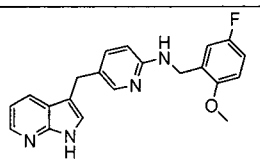
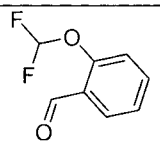
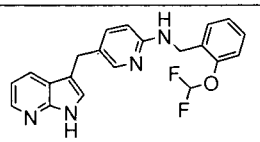
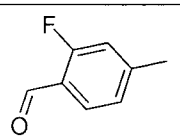
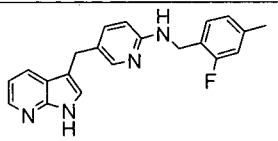
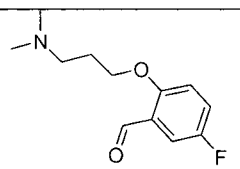
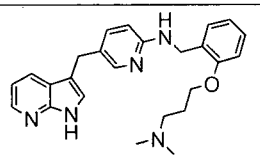
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0346			401.1
P-0347			401.1
P-0348			417.1
P-0349			417.1
P-0350			401.1
P-0351			383.1
P-0352			363.1
P-0353			360.3

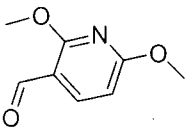
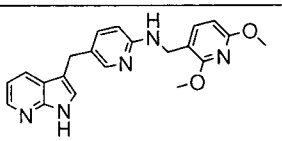
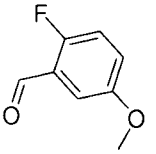
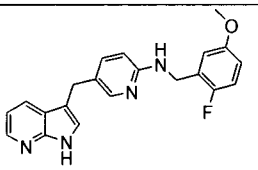
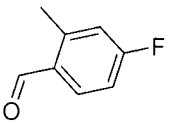
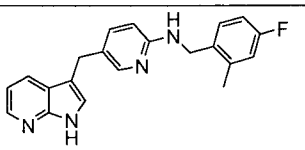
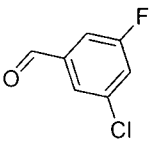
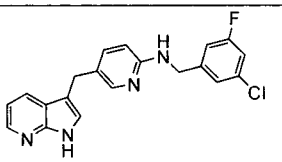
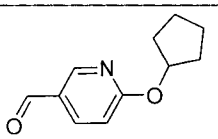
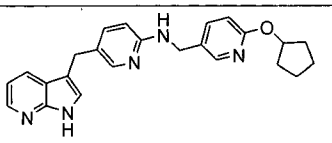
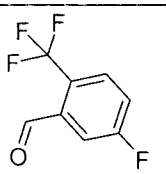
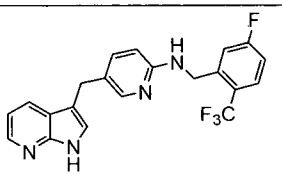
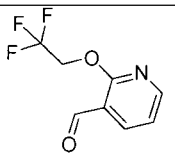
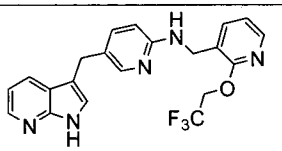
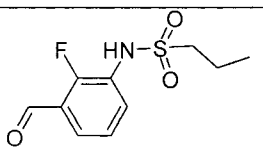
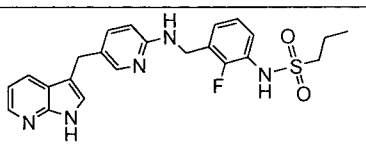
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0354			367.1
P-0355			334.3
P-0356			351.1
P-0357			373.1
P-0358			400.3
P-0359			379.1
P-0360			401.1
P-0361			444.3

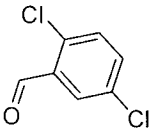
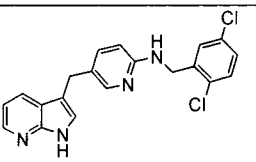
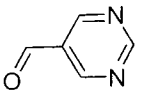
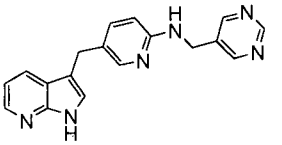
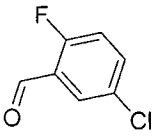
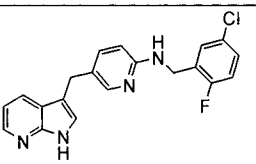
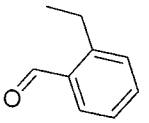
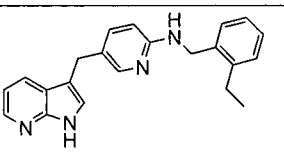
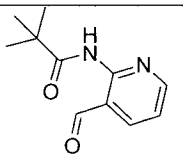
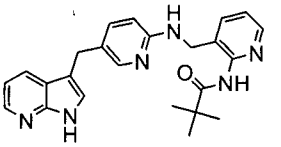
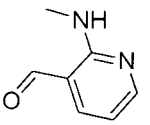
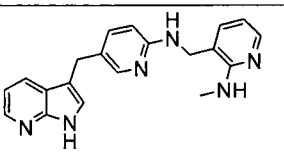
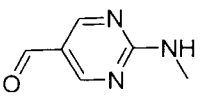
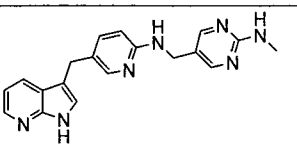
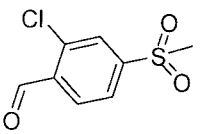
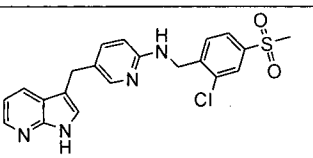
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0362			351.1
P-0363			417.1
P-0364			367.1
P-0365			401.1
P-0366			363.1
P-0367			381.1
P-0368			347.1
P-0369			416.3

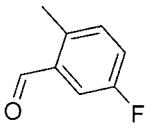
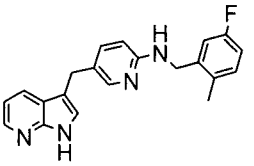
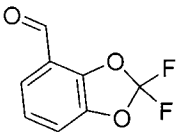
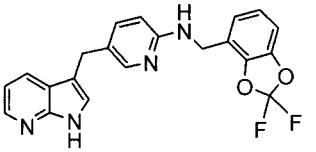
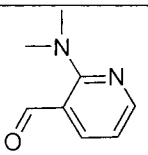
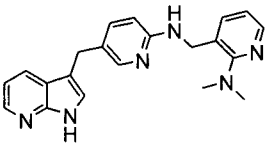
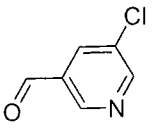
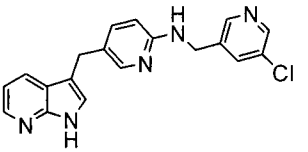
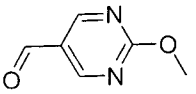
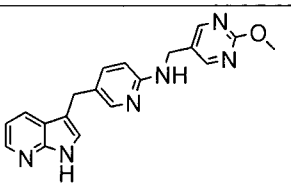
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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0370			376.3
P-0371			363.1
P-0372			347.1
P-0373			367.1
P-0374			400.3
P-0375			401.1
P-0376			413.9
P-0377			453.9

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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P0380			383.1
P-0381			317.2
P-0382			367.1
P-0383			343.1
P-0384			415.2
P-0385			345.4
P-0386			345.2
P-0387			427.1

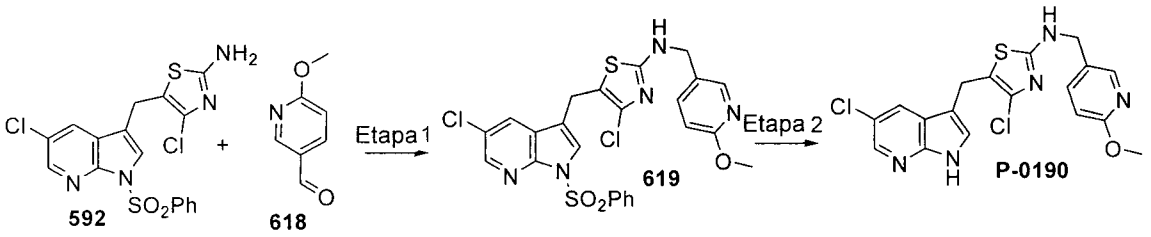
369

Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0397			347.1
P-0398			396.1
P-0399			359.1
P-0400			350.3
P-0401			347.1

Ejemplo 40: Síntesis de [4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina P-0190

[0280] [4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina P-0190 se sintetizó en 2 etapas a partir de 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **592** como se muestra en el Esquema 196.

Esquema 196



*Etapa I – Preparación de [5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**619**):*

[0281] 5-(1-Bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina (**592**, 30 mg, 0.083 mmol, preparada como se describe en el Ejemplo 27, Esquema 183) se combinó con 6-metoxi-piridina-3-carbaldehído (**618**, 26.2 mg, 0.165 mmol) en un vial de reacción para microondas de 2 ml. La mezcla se disolvió en etanol: ácido acético (95:5, 0.6 ml). Cianoborohidruro soportado en sílice (1.0 mmol/g, 83 mg, 0.083 mmol) se agregó y la mezcla se irradió con microondas a 300 watts durante 5 minutos a 100 °C. La sílice se separó por centrifugación y el sobrenadante en solución se decantó. El residuo de sílice se enjuagó con etanol (0.500 ml) y se centrifugó. Los solventes se combinaron y removieron bajo presión reducida para dar el compuesto deseado **619**, que se usó sin purificación posterior.

*Etapa II – Preparación de [4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina (**P-0190**):*

[0282] [5-(1-Bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina **619** se combinó con metanol: hidróxido de potasio (1M) (1:1, 0.5 ml). La mezcla se calentó a 80 °C durante 2 horas. Ácido acético (0.1 ml) se agregó y los solventes se removieron bajo presión reducida. El residuo restante se disolvió en dimetilsulfóxido (0.4 ml) y se purificó por HPLC de fase inversa en una columna Phenomenex (50mm x 10mm ID) eluyendo con 0.1 % de ácido trifluoroacético en agua y 20-100 % de acetonitrilo con 0.1% de ácido trifluoroacético durante 16 minutos a un flujo volumétrico de 6 ml/minuto para proporcionar el compuesto deseado **P-0190**. MS (ESI) $[M+H^+]^+ = 419.9$.

[0283] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 196, reemplazando 6-metoxi-piridina-3-carbaldehído **618** con un aldehído adecuado en la Etapa 1. Los siguientes compuestos se produjeron siguiendo este procedimiento:

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-tiazol-2-ilmetil-amina (**P-0189**),

Bencil-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-0192**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-metoxi-bencil)-amina (**P-0193**),

(4-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-0194**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina (**P-0195**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina (**P-0196**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina (**P-0197**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-2H-pirazol-3-ilmetil)-amina (**P-0198**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina (**P-0199**),

[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]-(2-metil-tiazol-4-ilmetil)-amina (**P-0201**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-metil-tiazol-5-ilmetil)-amina (**P-0202**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-cloro-piridin-2-ilmetil)-amina (**P-0203**),

[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]-piridin-4-ilmetil-amina (**P-0237**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-cloro-piridin-4-ilmetil)-amina (**P-0238**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1-etil-1H-pirazol-4-ilmetil)-amina (**P-0239**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina (**P-**

Patente de Invención

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[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-cloro-6-fluoro-bencil)-amina (**P-0243**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-fenetil-amina (**P-0244**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-difluoro-bencil)-amina (**P-0245**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-fluoro-bencil)-amina (**P-0246**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina (**P-0247**),

(2-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina (**P-0248**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-bencil)-amina (**P-0249**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-cloro-4-fluoro-bencil)-amina (**P-0250**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-2-ilmetil)-amina (**P-0251**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina (**P-0252**),

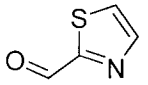
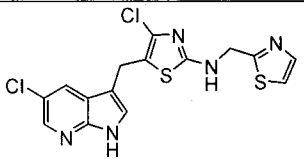
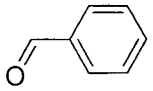
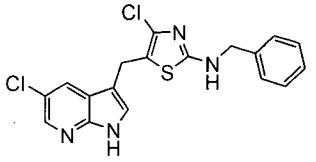
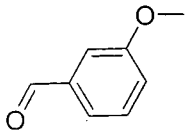
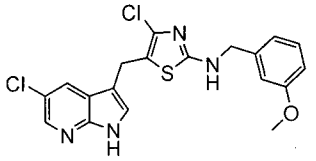
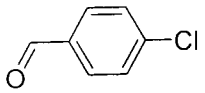
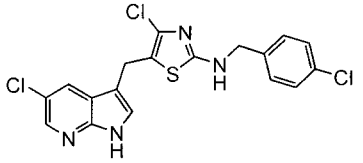
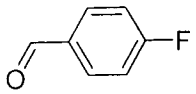
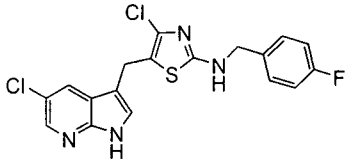
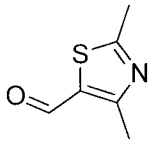
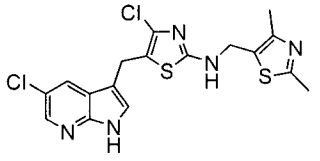
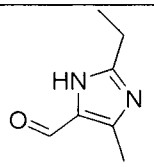
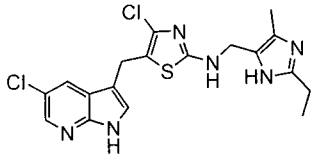
[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3,5-dicloro-piridin-4-ilmetil)-amina (**P-0253**),

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-trifluorometil-bencil)-amina (**P-0254**), y

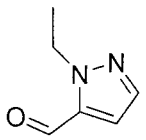
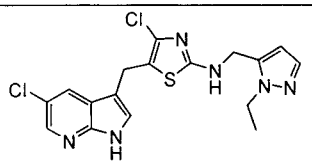
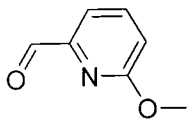
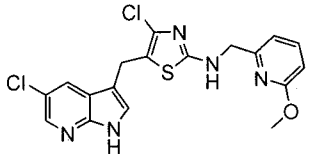
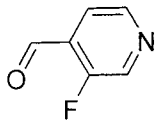
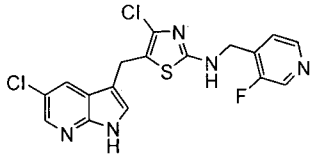
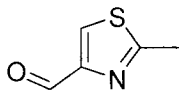
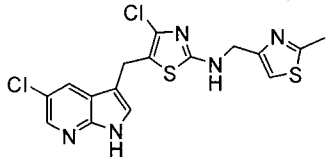
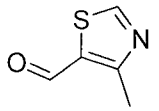
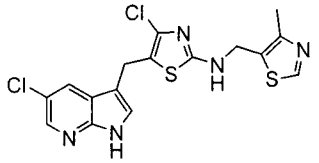
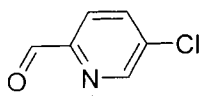
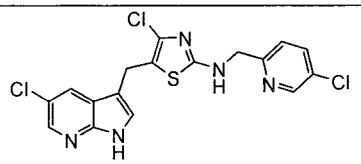
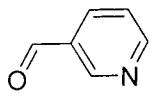
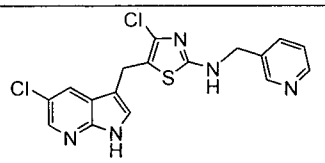
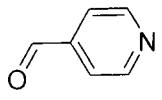
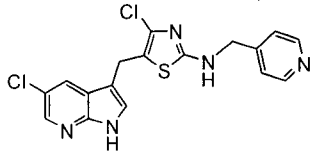
[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina (**P-0255**).

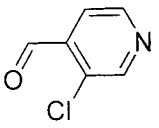
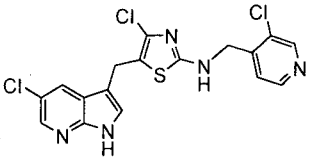
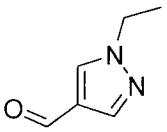
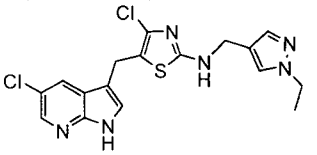
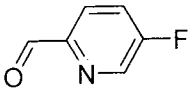
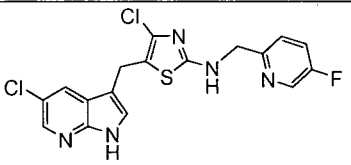
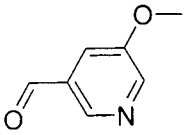
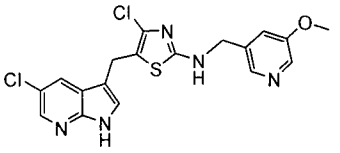
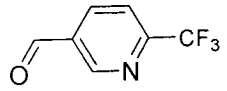
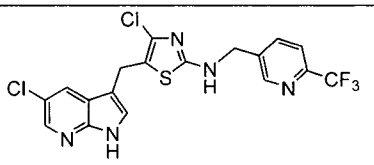
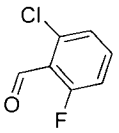
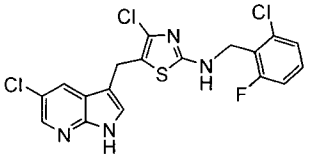
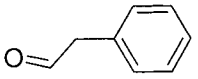
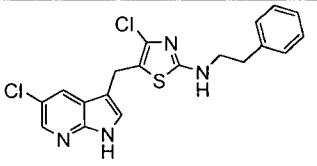
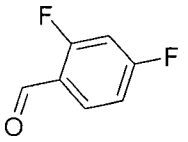
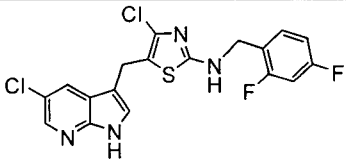
La siguiente tabla indica el aldehído (Columna 2) usado en la Etapa 1 del Esquema 196 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la

Columna 4 el resultado experimental de la espectrometría de masas.

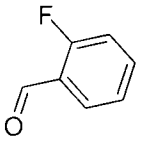
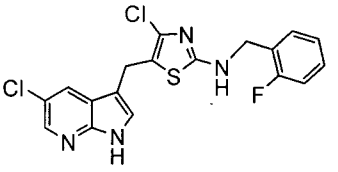
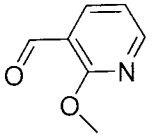
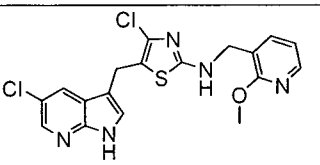
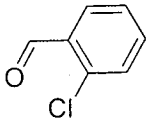
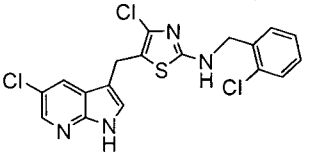
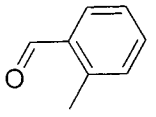
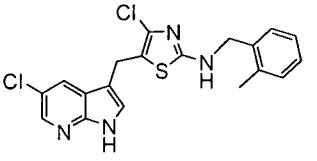
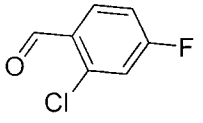
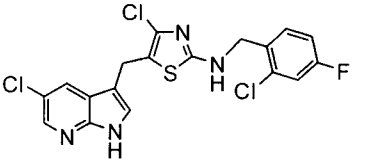
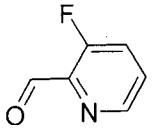
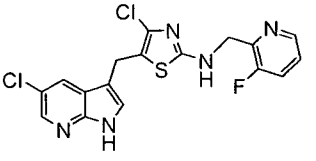
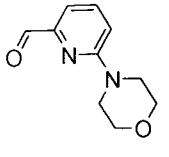
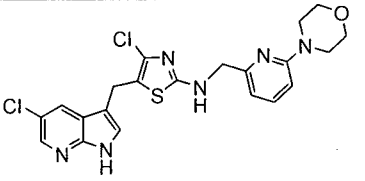
Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0189			395.9
P-0192			389.1
P-0193			419.1
P-0194			425.1
P-0195			407.1
P-0196			423.9
P-0197			421.1

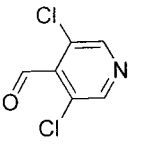
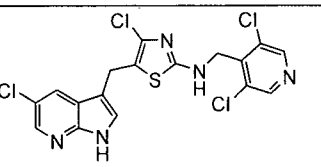
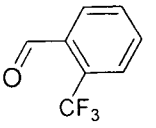
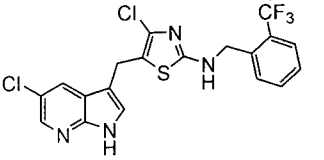
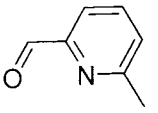
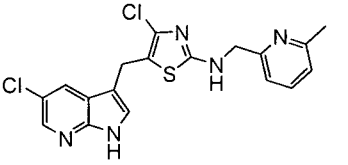
374

Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0198			407.1
P-0199			419.9
P-0200			407.9
P-0201			409.9
P-0202			409.9
P-0203			423.9
P-0236			390.3
P-0237			390.3

Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0238			425.9
P-0239			407.1
P-0240			407.9
P-0241			419.9
P-0242			458.3
P-0243			443.1
P-0244			403.1
P-0245			424.7

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Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0246			407.1
P-0247			419.9
P-0248			424.7
P-0249			403.1
P-0250			441.1
P-0251			407.9
P-0252			475.1

Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0253			459.9
P-0254			457.1
P-0255			404.3

[0284] Compuestos adicionales se prepararon siguiendo el protocolo del Esquema 196, reemplazando 5-(1-bencensulfonil-5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **592** con 5-(1-bencensulfonil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-4-cloro-tiazol-2-ilamina **593** (preparada como se describe en el Ejemplo 27, Esquema 183) además de reemplazar 6-metoxi-piridina-3-carbaldehído **618** con un aldehído adecuado en la Etapa 1. Los siguientes compuestos se produjeron siguiendo este procedimiento:

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina (**P-0204**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina (**P-0205**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina (**P-0206**),

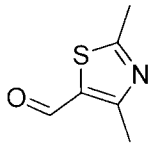
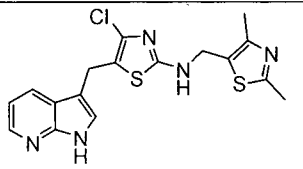
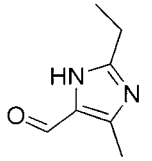
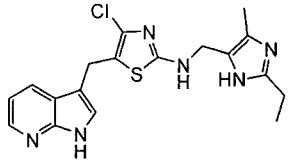
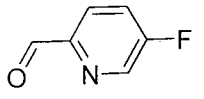
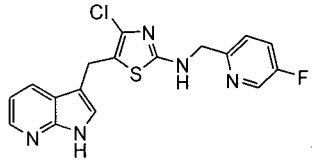
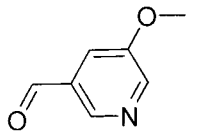
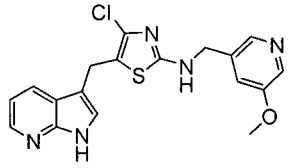
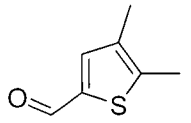
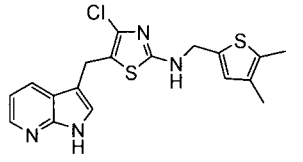
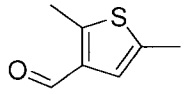
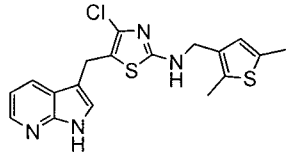
[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina (**P-0207**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4,5-dimetil-tiofen-2-ilmetil)-amina (**P-0208**),

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-tiofen-3-ilmetil)-amina (**P-0209**),

La siguiente tabla indica el aldehído (Columna 2) usado en la Etapa 1 del Esquema 196 para proporcionar los compuestos (Columna 3). La Columna 1 proporciona el número de compuesto y la

Columna 4 el resultado experimental de la espectrometría de masas.

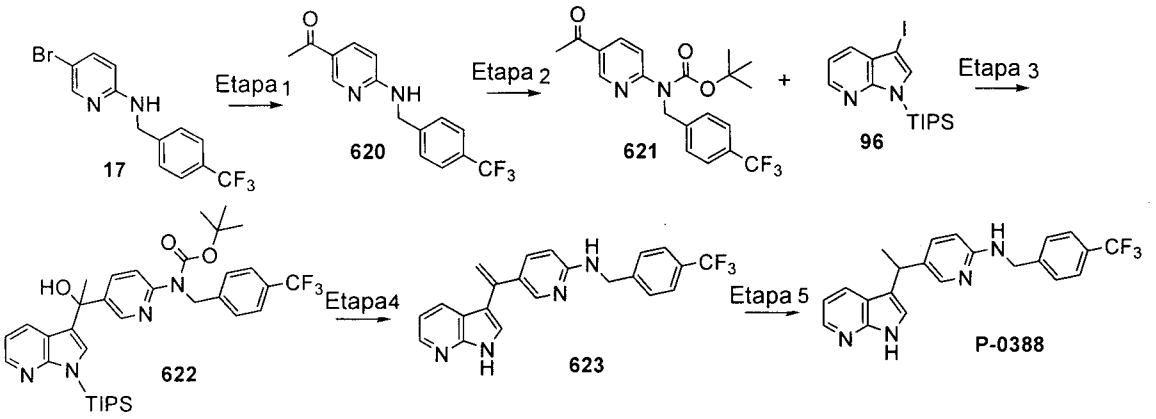
Número de compuesto	Aldehído	Compuesto	MS(ESI) $[M+H^+]^+$ observada
P-0204			390.3
P-0205			387.1
P-0206			373.9
P-0207			386.3
P-0208			389.1
P-0209			389.1

Ejemplo 41: Síntesis de 5-[1-(1H-pirrolo[2,3-b]piridin-3-il)-etil]-piridin-2-il-(4-trifluorometil-bencil)-amina P-0388

[0285] 5-[1-(1H-Pirrolo[2,3-b]piridin-3-il)-etil]-piridin-2-il-(4-trifluorometil-bencil)-amina **P-0388** se sintetizó a partir de (5-bromo-piridin-2-il)-(4-trifluorometil-bencil)-amina **17** como se muestra en el

Esquema 197.

Esquema 197



*Etapa 1 - Preparación de 1-[6-(4-trifluorometil-bencilamino)-piridin-3-il]-etanona (**620**):*

[0286] (5-Bromo-piridin-2-il)-(4-trifluorometil-bencil)-amina (**17**, 3.00 g, 9.06 mmol) se disolvió en tetrahidrofurano (80 ml). La reacción se enfrió a -78 °C bajo una atmósfera de argón. 2.5 M de n-butilitio en hexano (10.9 ml) se agregó. La reacción se agitó a -78 °C durante 60 minutos. N-Metoxi-N-metilacetamida (1.93 ml, 18.1 mmol) se agregó a la reacción, que se dejó entibiar a temperatura ambiente. La reacción se vertió en 1M de cloruro de amonio y salmuera y se extrajo con acetato de etilo. Las porciones orgánicas se secaron con sulfato de sodio anhidro, se filtraron y el filtrado se adsorbió sobre sílice. La mezcla se purificó por cromatografía en gel de sílice (acetato de etilo:hexanos) para proporcionar el compuesto deseado como un aceite que cristalizó a un sólido blanco (**620**, 1.328 g, 50%), consistente con la estructura del compuesto por ^{1}H-NMR y MS(ESI): $[M+H^+]^+$=295.3.

*Etapa 2 - Preparación de ter-butiléster del ácido (5-acetil-piridin-2-il)-(4-trifluorometil-bencil)-carbámico (**621**):*

[0287] A 1-[6-(4-trifluorometil-bencilamino)-piridin-3-il]-etanona (**620**, 1.30 g, 4.42 mmol) en tetrahidrofurano (15.0 ml) se agregaron di-ter-butildicarbonato (1.10 g, 5.04 mmol), 4-dimetilaminopiridina (0.0259 g, 0.21 mmol) y N,N-diisopropiletilamina (0.888 ml, 5.10 mmol) bajo una atmósfera de nitrógeno. La reacción se agitó a temperatura ambiente durante 3 días. La mezcla se extrajo con acetato de etilo y bicarbonato de sodio saturado. Las porciones orgánicas se secaron con sulfato de sodio anhidro, se filtraron y el filtrado se adsorbió sobre sílice. La mezcla se

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purificó por cromatografía en gel de sílice (0-15% de acetato de etilo:hexanos) para proporcionar el compuesto deseado como un aceite que solidificó a un sólido blanco (**621**, 1.29g, 74%), consistente con la estructura del compuesto por ^{1}H-NMR.

*Etapa 3 - Preparación de 1-[6-(4-trifluorometil-bencilamino)-piridin-3-il]-1-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-etanol (**622**):*

[0288] 3-Yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina (**96**, 485.9 mg, 1.21 mmol) se disolvió en tetrahidrofurano (8 ml) a -20 °C bajo una atmósfera de nitrógeno. 2.0 M de cloruro de isopropilmagnesio en tetrahidrofurano (0.655 ml) se agregó. La reacción se agitó a -20 °C durante 1 hora. En la reacción se agregó ter-butiléster del ácido (5-acetil-piridin-2-il)-(4-trifluorometil-bencil)-carbámico (**621**, 300.0 mg, 0.76 mmol) en tetrahidrofurano (6 ml) La reacción se dejó entibiar a temperatura ambiente durante la noche. La mezcla se extrajo con acetato de etilo y bicarbonato de sodio saturado. Las porciones orgánicas se secaron con sulfato de sodio anhidro, se filtraron y el filtrado se adsorbió sobre sílice. La mezcla se purificó por cromatografía en gel de sílice (acetato de etilo:hexanos), para proporcionar el compuesto deseado como un aceite (**622**, 125 mg, 29%), consistente con la estructura del compuesto por ^{1}H-NMR.

*Etapa 4 - Preparación de 5-[1-(1H-pirrolo[2,3-b]piridin-3-il)-vinil]-piridin-2-il-(4-trifluorometil-bencil)-amina (**623**):*

[0289] 1-[6-(4-Trifluorometil-bencilamino)-piridin-3-il]-1-(1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-etanol (**622**, 125.0 mg, 0.22 mmol) se disolvió en acetonitrilo (11.7 ml) y ácido trifluoroacético (0.175 ml, 2.3 mmol) y trietilsilano (0.292 ml, 1.8 mmol) se agregaron. La reacción se calentó a reflujo durante la noche. La reacción se concentró, luego se lavó con acetato de etilo y bicarbonato de sodio saturado. Las porciones orgánicas se secaron con sulfato de sodio anhidro, se filtraron y el filtrado se adsorbió sobre sílice. La mezcla se purificó por cromatografía en gel de sílice (0-60% de acetato de etilo:hexanos) para proporcionar el compuesto deseado (**623**, 43 mg, 50%), consistente con la estructura del compuesto por ^{1}H-NMR.

*Etapa 5 - Preparación de 5-[1-(1H-pirrolo[2,3-b]piridin-3-il)-etil]-piridin-2-il-(4-trifluorometil-bencil)-amina (**P-0388**):*

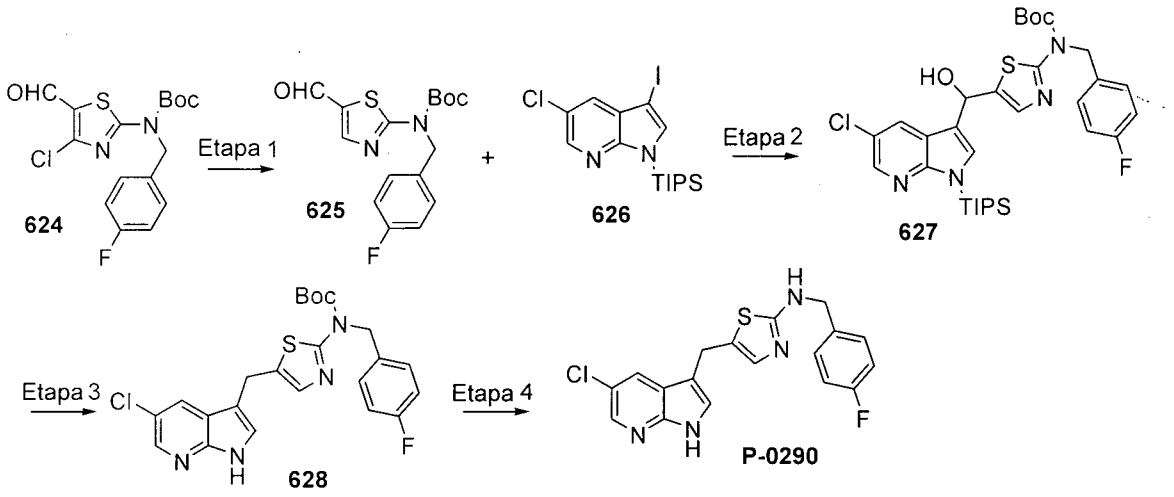
[0290] 5-[1-(1H-Pirrolo[2,3-b]piridin-3-il)-vinil]-piridin-2-il-(4-trifluorometil-bencil)-amina (**623**, 0.043

g, 0.00011 mol) se disolvió en tetrahidrofurano (10 ml) y metanol (10 ml). La reacción se agitó bajo una atmósfera de hidrógeno (206.8 kPa (30 psi)) durante la noche. La reacción se filtró a través de Celite y el filtrado se adsorbió sobre sílice y se purificó por cromatografía de columna en gel de sílice (acetato de etilo:hexanos) para proporcionar el compuesto deseado como un sólido blanco (**P-0388**, 2.1 mg, 5%), consistente con la estructura del compuesto por ^{1}H-NMR y MS(ESI): $[M+H^+]^+$=397.6.

Ejemplo 42: Síntesis de [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina P-0290

[0291] [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina **P-0290** se sintetizó en cuatro etapas a partir de (4-fluoro-bencil)-ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico **624** como se muestra en el Esquema 198.

Esquema 198



*Etapa 1 - Preparación de (4-fluoro-bencil)-ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**625**):*

[0292] A una solución de (4-fluoro-bencil)-ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**624**, 1 g, 2.70 mmol, preparada como se describe en el Ejemplo 5, Esquema 159, Etapa 2, donde 4-(aminometil)piridina **516** se reemplaza con p-fluorobencilamina, es decir, el intermediario en la preparación del compuesto **P-0156**) en metanol (100 ml) se agregó Pd/C (100 mg, 50% de agua) y acetato de sodio (660 mg, 8.09 mmol) y la mezcla se agitó bajo una atmósfera de hidrógeno (344.7 kPa (50 psi)) durante la noche observando ~50% de conversión por LC/MS.

La mezcla se filtró sobre un lecho de Celite y el solvente se removió *in vacuo* y se purificó por cromatografía en gel de sílice (acetato de etilo/heptano) para proporcionar el compuesto deseado como un sólido blanquecino (450 mg, 50 %), consistente con la estructura del compuesto por ^{1}H-NMR.

*Etapa 2 - Preparación de ter-butiléster del ácido {5-[(5-cloro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-tiazol-2-il}-(4-fluoro-bencil)-carbámico (**627**):*

[0293] A una solución de 5-cloro-3-yodo-1-(triisopropilsilil)-1H-pirrolo[2,3-b]piridina (**626**, 300 mg, 0.69 mmol) en tetrahidrofurano (10 ml) a -20 °C se agregó por goteo cloruro de iso-propil-magnesio (2M en tetrahidrofurano, 0.44 ml, 0.88 mmol). La mezcla de reacción se dejó entibiar a 0 °C durante 10 minutos y luego se enfrió a -40 °C. A esta mezcla de reacción se agregó una solución de (4-fluoro-bencil)-ter-butiléster del ácido (4-cloro-5-formil-tiazol-2-il)-carbámico (**625**, 211 mg, 0.63 mmol) en tetrahidrofurano (5 ml). La mezcla de reacción se dejó entibiar a 0 °C durante 30 minutos y luego se extinguió con salmuera (50 ml). La mezcla se transfirió a un embudo de separación y las capas se separaron. La capa orgánica se secó sobre sulfato de sodio y se evaporó *in vacuo* para dar el material sin purificar que se purificó por cromatografía de columna en gel de sílice (0-30% de acetato de etilo/heptano) para proporcionar el compuesto deseado como una espuma (120 mg, 30%), consistente con la estructura por ^{1}H-NMR.

*Etapa 3 - Preparación de ter-butiléster del ácido [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-carbámico (**628**):*

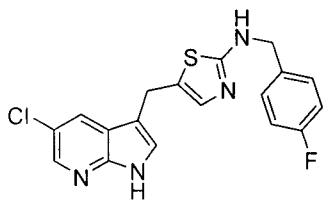
[0294] A una solución de ter-butiléster del ácido {5-[(5-cloro-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridin-3-il)-hidroxi-metil]-tiazol-2-il}-(4-fluoro-bencil)-carbámico (**627**, 120 mg, 0.186 mmol) en acetonitrilo (3 ml) se agregó ácido trifluoroacético (0.14 ml, 1.86 mmol) y trietilsilano (0.30 ml, 1.86 mmol). La mezcla resultante se agitó durante 2 horas a 40 °C. El solvente luego se removió *in vacuo* y el residuo se usó directamente en la siguiente etapa.

*Etapa 4: Preparación de [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina (**P-0290**):*

[0295] A la solución de ter-butiléster sin purificar del ácido [5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-carbámico (**628**, 0.186 mmol en teoría) en diclorometano (5 ml) a

temperatura ambiente se agregó ácido trifluoroacético (1 ml) y la reacción se dejó agitar durante la noche. El solvente se removió *in vacuo* y el residuo se recogió en acetato de etilo y luego se lavó con carbonato de potasio acuoso saturado cerciorándose de que se alcanzó la alcalinidad. Las capas se separaron y la capa acuosa se extrajo de nuevo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron *in vacuo* para dar el producto sin purificar que se purificó por cromatografía en gel de sílice (0-10% de metanol/acetato de etilo). El solvente se removió *in vacuo* y el material se trituró con diclorometano para dar el compuesto deseado como un sólido blanquecino (20 mg, 29 % durante 2 etapas) consistente con la estructura del compuesto por ^{1}H-NMR y MS(ESI): $[M+H^+]^+$=372.9.

[0296] (4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina **P-0389**



se sintetizó siguiendo el protocolo del Esquema 198, reemplazando 5-cloro-3-yodo-1-(triisopropilsilil)-1H-pirrolo[2,3-b]piridina **626** con 3-yodo-1-triisopropilsilanil-1H-pirrolo[2,3-b]piridina **96**, para proporcionar el compuesto deseado, consistente con la estructura por 1H-NMR y MS(ESI): $[M+H^+]^+$=339.0.

Ejemplo 43: Compuestos adicionales

[0297] Los siguientes compuestos de la invención se sintetizaron siguiendo los métodos de los ejemplos anteriormente, o métodos similares conocidos por los expertos en la técnica:

(5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-[2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-il]-metanona (**P-0184**),

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-etil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina (**P-0185**),

(3-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina (**P-0410**),

y

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(2,5-difluoro-bencil)-amina (**P-0411**).

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Ejemplo 44: Ensayos de actividad enzimática

[0298] Ensayos para la actividad de c-Kit o c-Fms se conocen en la técnica, por ejemplo como se describe en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519, cuya descripción se incorpora por la presente como referencia en su totalidad. Ensayos similares pueden usarse para valorar la actividad de TrkA, TrkB, y HGK.

[0299] Ensayos adicionales basados en células pueden correlacionarse con la actividad de Fms de los compuestos de la invención. Por ejemplo, la capacidad de las células precursoras de osteoclastos (comercialmente disponibles de Lonza) para diferenciarse a osteoclastos maduros, debido a la estimulación por M-CSF y RANKL, en presencia de los compuestos, puede medirse usando un método análogo a aquel previamente reportado (Hudson et al., Journal of Urology, 1947, 58:89-92), donde la cantidad de fosfatasa ácida en el sobrenadante (es decir, TRAP5b excretada por osteoclastos maduros) es proporcional al número de osteoclastos maduros presentes. En otro ejemplo, la capacidad de los macrófagos murinos dependientes de M-CSF (BAC1.2F5) para proliferar en presencia de los compuestos puede medirse al cultivar células como se describe previamente (Morgan et al., Journal of Cellular Physiology, 1987, 130:420-427) y determinar la viabilidad celular por análisis de niveles de ATP en el cultivo celular (Crouch et al., Journal of Immunological Methods, 1993, 160:81-8).

[0300] Los compuestos P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0107, P-0108, P-0109, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0118, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0131, P-0132, P-0138, P-0143, P-0144, P-0145, P-0148, P-0154, P-0156, P-0157, P-0159, P-0161, P-0163, P-0170, P-0171, P-0173, P-0174, P-0176, P-0177, P-0179, P-0180, P-0181, P-0182, P-0186, P-0187, P-0188, P-0190, P-0192, P-0193, P-0194, P-0195, P-0197, P-0199, P-0201, P-0203, P-0205, P-0206, P-0208, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0221, P-0222, P-0224, P-0225, P-0226, P-0228, P-0234, P-0237, P-0239, P-0240, P-0242, P-0243, P-0244, P-0245, P-0246, P-0252, P-0253, P-0255, P-0257, P-0258, P-0259, P-0260, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281,

P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0294, P-0297, P-0298, P-0301, P-0302, P-0303, P-0305, P-0306, P-0307, P-0308, P-0309, P-0311, P-0312, P-0313, P-0314, P-0316, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0334, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0350, P-0351, P-0352, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0361, P-0362, P-0363, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0375, P-0376, P-0377, P-0378, P-0379, P-0382, P-0383, P-0385, P-0387, P-0390, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0404, P-0406, P-0407, P-0408, P-0409, y P-0412 demostraron una IC_{50} de menos de 1 μM en al menos uno de los ensayos de c-kit descritos en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519.

[0301] Los compuestos P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0106, P-0107, P-0108, P-0109, P-0110, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0117, P-0118, P-0119, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0130, P-0131, P-0132, P-0134, P-0135, P-0136, P-0137, P-0140, P-0141, P-0142, P-0143, P-0144, P-0145, P-0146, P-0147, P-0148, P-0149, P-0150, P-0151, P-0152, P-0153, P-0154, P-0156, P-0157, P-0158, P-0159, P-0160, P-0161, P-0163, P-0164, P-0165, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0175, P-0176, P-0179, P-0180, P-0181, P-0182, P-0183, P-0185, P-0186, P-0187, P-0188, P-0189, P-0190, P-0191, P-0192, P-0193, P-0194, P-0195, P-0196, P-0197, P-0198, P-0199, P-0200, P-0201, P-0202, P-0203, P-0204, P-0205, P-0206, P-0207, P-0208, P-0209, P-0210, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0232, P-0233, P-0234, P-0235, P-0236, P-0237, P-0238, P-0239, P-0240, P-0241, P-0242, P-0243, P-0244, P-0245, P-0246, P-0247, P-0248, P-0249, P-0250, P-0251, P-0252, P-0253, P-0254, P-0255, P-0256, P-0257, P-0258, P-0259, P-0260, P-0261, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0292,

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P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0299, P-0300, P-0301, P-0302, P-0303, P-0304, P-0305, P-0306, P-0307, P-0308, P-0309, P-0310, P-0311, P-0312, P-0313, P-0314, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0333, P-0334, P-0335, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0349, P-0350, P-0351, P-0352, P-0353, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0360, P-0361, P-0362, P-0363, P-0364, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0374, P-0375, P-0376, P-0377, P-0378, P-0379, P-0380, P-0381, P-0382, P-0383, P-0384, P-0385, P-0386, P-0387, P-0390, P-0391, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0403, P-0404, P-0405, P-0406, P-0407, P-0408, P-0409, y P-0412 tuvieron IC_{50} de menos de 1 μM en al menos uno de los ensayos de Fms descritos en la Publicación de Solicitud de Patente Estadounidense número US 2007/0032519.

[0302] Los compuestos se probaron de manera similar para determinar valores de IC_{50} con respecto a la inhibición de actividad de cinasa TrkA, para lo cual los compuestos P-0157, P-0171, P-0179, P-0180, P-0303 y P-0412 tuvieron IC_{50} de menos de 1 μM. en este ensayo de TrkA. Los compuestos se probaron de manera similar para determinar valores de IC_{50} con respecto a la inhibición de actividad de cinasa HGK, para lo cual los compuestos P-0156, P-0177, P-0179, P-0195, P-0201, P-0203, P-0206, P-0207, P-0231, P-0240, P-0241, P-0255, P-0324, P-0341, y P-0403 tuvieron IC_{50} de menos de 1 μM.

[0303] Todas las patentes y otras referencias citadas en la especificación son indicativas del nivel de experiencia de los expertos en la técnica a la cual pertenece la invención, y se incorporan como referencia en sus totalidades, incluyendo cualesquier tablas y figuras, en la misma magnitud como si cada referencia se hubiera incorporado como referencia en su totalidad individualmente.

[0304] 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 representativos actualmente de las modalidades preferidas son ejemplares y no pretenden ser limitaciones sobre el alcance de la invención. A los expertos en la técnica se les ocurrirán cambios acerca de ello y otros

usos, que se abarcan dentro del espíritu de la invención, y que se definen por el alcance de las reivindicaciones.

[0305] Será fácilmente aparente para un experto en la técnica que pueden hacerse sustituciones y modificaciones variables a la invención descrita en este documento sin apartarse del alcance y espíritu de la invención. Por ejemplo, pueden hacerse variaciones para proporcionar compuestos adicionales de la Fórmula I y/o pueden usarse diversos métodos de administración. De esta manera, tales modalidades adicionales están dentro del alcance de la presente invención y las siguientes reivindicaciones.

[0306] La invención ilustrativamente descrita en este documento puede practicarse de manera adecuada en ausencia de cualquier elemento o elementos, limitación o limitaciones que no se describan específicamente en este documento. Los términos y expresiones que se han empleado se usan como términos de descripción y no de limitación, y no hay intención, en el uso de tales términos y expresiones, de excluir 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, puede recurrirse a la modificación y variación de los conceptos en este documento descrito 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.

[0307] Además, donde se describen atributos o aspectos de la invención en términos de grupos de Markush u otra agrupación de alternativas, los expertos en la técnica reconocerán que la invención también se describe en consecuencia en términos de cualquier miembro individual o subgrupo de miembros del grupo de Markush u otro grupo.

[0308] También, a menos que se indique lo contrario, donde se proporcionan diversos valores numéricos para las modalidades, se describen modalidades adicionales al tomar cualesquier 2 valores diferentes como los puntos finales de un intervalo. Tales intervalos también están dentro del alcance de la invención descrita.

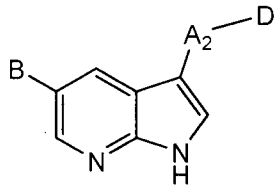
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[0309] De esta manera, las modalidades adicionales están dentro del alcance de la invención y dentro de las siguientes reivindicaciones.

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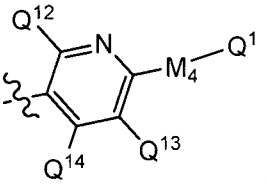
REIVINDICACIONES

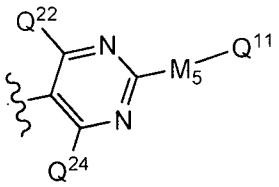
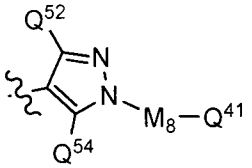
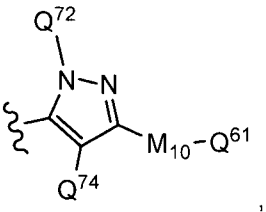
1. Un compuesto que tiene la estructura química de la Fórmula II,

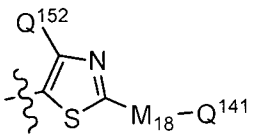


todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

D tiene una estructura seleccionada del grupo que consiste de  ,

 ,  ,  , y



en que  indica el punto de unión de D a A_2 de la Fórmula II;

A_2 es $-CH_2-$ o -C(O)-;

B se selecciona del grupo que consiste de hidrógeno, -CN, $-OR^{41}$, $-SR^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halógeno, alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo como B, o como sustituyentes de alquilo inferior, se

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sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

M_4 es $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, o $-NR^{39}C(O)-$;

M_5, M_{10}, y M_{18} se seleccionan del grupo que consiste de un enlace, $-NR^{39}-$, -S-, -O-, $-NR^{39}CH_2-$, $-NR^{39}CH_2CH_2-$, $-NR^{39}CH(R^{40})-$, $-SCH_2-$, $-OCH_2-$, $-C(O)NR^{39}-$, $-S(O)_2NR^{39}-$, $-CH_2NR^{39}-$, $-CH(R^{40})NR^{39}-$, $-NR^{39}C(O)-$, y $-NR^{39}S(O)_2-$;

M_8 se selecciona del grupo que consiste de un enlace, $-CH_2-$, $-CH_2C(O)-$, $-S(O)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2CH_2CH_2-$, $-S(O)_2NR^{39}-$, $-S(O)_2NR^{39}CH_2-$, $-S(O)_2NR^{39}CH(CH_3)-$, $-S(O)_2NR^{39}CH_2CH_2-$, -C(O)-, $-C(O)CH_2-$, $-C(O)CH(CH_3)-$, $-C(O)CH_2CH_2-$, $-C(O)NR^{39}-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, y $-C(O)NR^{39}CH_2CH_2-$;

Q^1, Q^{11}, Q^{41}, Q^{61}, y Q^{141} son arilo o heteroarilo opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste de $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halógeno, alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo como Q^1, Q^{11}, Q^{41}, Q^{61}, o Q^{141}, o como sustituyente de alquilo inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

Q^{12} es flúor, cloro o $-CF_3$;

Q^{13} y Q^{14} son independientemente hidrógeno, flúor, cloro, alquilo inferior, o alquilo inferior sustituido con flúor;

Q^{22}, Q^{24}, Q^{52}, y Q^{54} se seleccionan independientemente del grupo que consiste de hidrógeno,

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halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NR^{44}R^{44}$, $-OR^{44}$, y $-SR^{44}$, siempre y cuando, sin embargo, al menos uno de Q^{22} y Q^{24} y al menos uno de Q^{52} y Q^{54} sea hidrógeno, flúor, cloro, alquilo inferior o alquilo inferior sustituido con flúor;

Q^{74} y Q^{152} son hidrógeno, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, $-NR^{44}R^{44}$, $-OR^{44}$, o $-SR^{44}$;

Q^{72} es hidrógeno, alquilo inferior o alquilo inferior sustituido con flúor;

R^{39} en cada caso es independientemente hidrógeno o alquilo inferior;

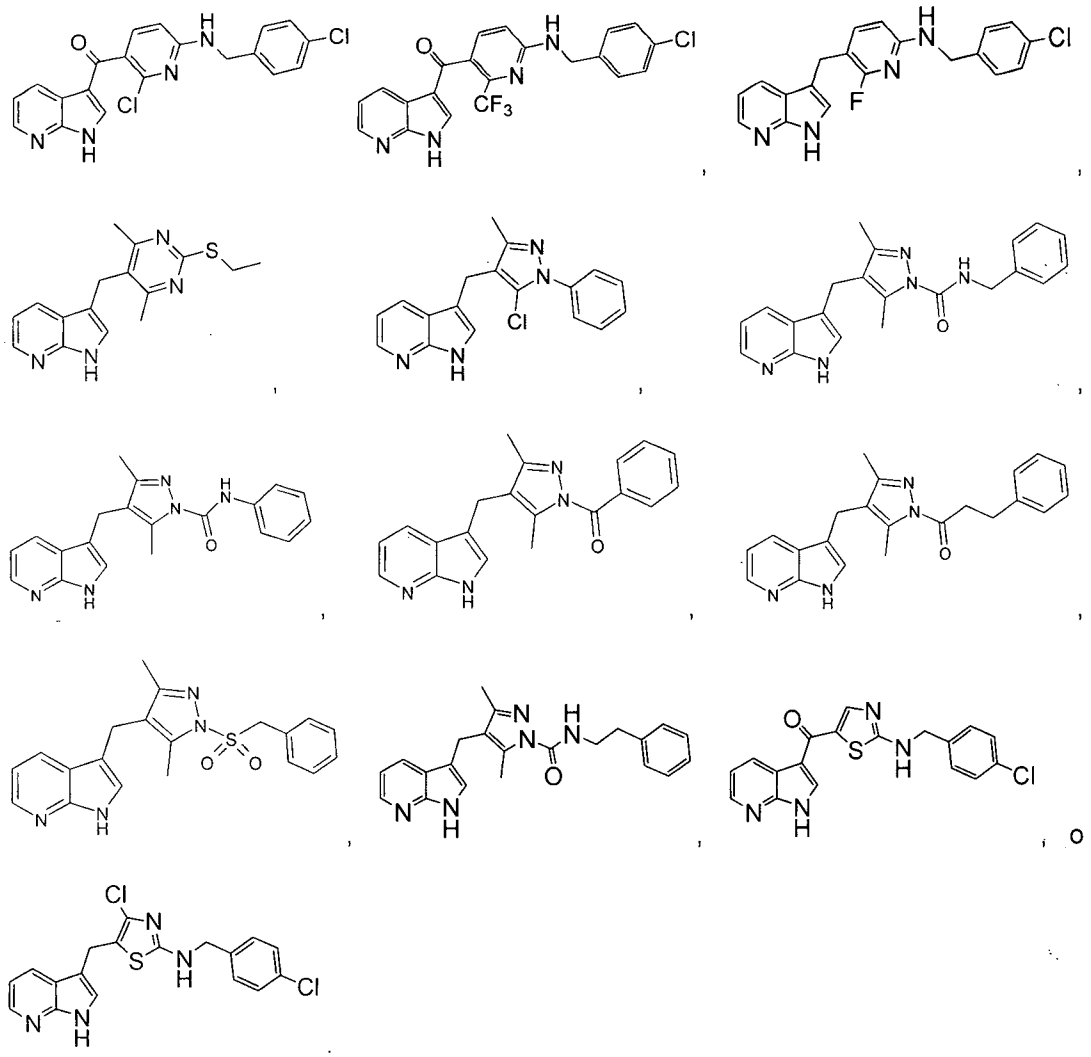
R^{40} es alquilo inferior o alquilo inferior sustituido con flúor;

R^{41} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, como R^{41} o como sustituyentes de alquilo inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino;

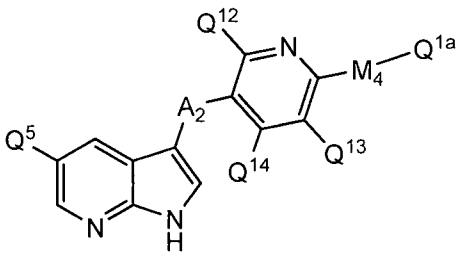
R^{42} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, heterocicloalquilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, y cicloalquilamino, y en donde el heterocicloalquilo y heteroarilo se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior y alcoxi inferior sustituido con flúor; y

cada R^{44} es independientemente hidrógeno, alquilo inferior o alquilo inferior sustituido con flúor; siempre y cuando, sin embargo, el compuesto no sea

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2. El compuesto de conformidad con la Reivindicación **1** que tiene la estructura de la Fórmula IIa,



todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

Q^{1a} es arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior,

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alquilo inferior sustituido con flúor, -NHR^{41}, -$NR^{41}R^{41}$, y -OR^{41};

Q^5 es hidrógeno, -CN, -OR^{41}, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, arilo o heteroarilo, en donde el arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, -NHR^{41}, -$NR^{41}R^{41}$, y -OR^{41}; y

A_2, M_4, Q^{12}, Q^{13}, Q^{14} y R^{41} son como se define para la Reivindicación 1.

3. El compuesto de conformidad con la Reivindicación **2** seleccionado del grupo que consiste de:

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-amina,

(4-Cloro-bencil)-[6-cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[6-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[6-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

{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,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[6-fluoro-5-(5-metoxi-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

3-{2-Cloro-6-[(6-trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[6-Cloro-5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

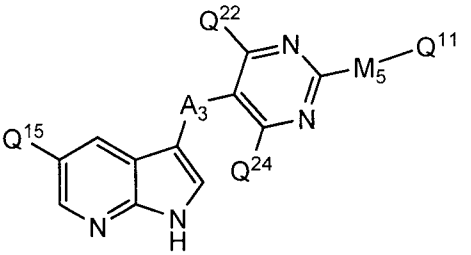
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[6-fluoro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-6-fluoro-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina; y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

4. Un compuesto de conformidad con la Reivindicación **1** que tiene la estructura de la Fórmula IIb



todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

A_3 es $-CH_2-$ o -C(O)-;

Q^{15} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

M_5, Q^{11}, Q^{22}, Q^{24}, y R^{41}, son como se define para la Fórmula II.

5. El compuesto de conformidad con la Reivindicación **4** seleccionado del grupo que consiste de:

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,6-difluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina,

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,4-difluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,5-difluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometil-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-5-trifluorometil-bencil)-amina,

(2-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-Cloro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(3-fluoro-5-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(3,5-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina,

(5-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2,4-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(4-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina,

(2-fluoro-3-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2,5-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina, (3-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-Difluorometoxi-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2,3-Dicloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(4-Cloro-2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(5-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(5-Cloro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(5-fluoro-2-metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

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(2-fluoro-4-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-difluorometoxi-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(5-fluoro-2-trifluorometil-bencil)-amina,

(3-Cloro-2-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-3-trifluorometil-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-4-trifluorometil-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,3-difluoro-bencil)-amina,

(2-Cloro-4-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometoxi-bencil)-amina,

(2-Cloro-5-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

(2-Cloro-5-fluoro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina; y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

6. El compuesto de conformidad con la Reivindicación **4** seleccionado del grupo que consiste de:

(4-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-trifluorometil-bencil)-amina,

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,4-difluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2,5-difluoro-bencil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(3-trifluorometil-bencil)-amina,

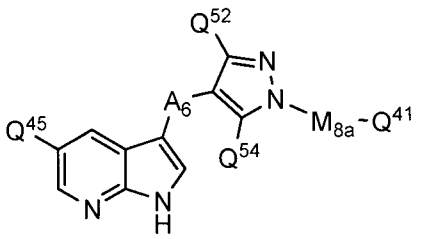
[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(2-fluoro-5-trifluorometil-bencil)-amina,

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[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-pirimidin-2-il]-(4-trifluorometil-bencil)-amina; y

todas las sales, profármacos, tautómeros, e isómeros de los mismos.

7. El compuesto de conformidad con la Reivindicación **1** que tiene la estructura química de la Fórmula IIe,



todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

A_6 es $-CH_2-$ o -C(O)-;

M_{8a} se selecciona del grupo que consiste de $-CH_2-$, $-CH_2C(O)-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(R^{40})-$, y $-C(O)NR^{39}CH_2CH_2-$;

Q^{45} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

Q^{41}, Q^{52}, Q^{54}, R^{39}, R^{40}, y R^{41} son como se define para la Reivindicación 1.

8. El compuesto de conformidad con la Reivindicación **7** seleccionado del grupo que consiste de:

3-(1-Bencil-3,5-dimetil-1H-pirazol-4-ilmetil)-1H-pirrolo[2,3-b]piridina,

2-[3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-il]-1-fenil-etanona,

4-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

2-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

2-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-

carboxílico,

3-[3,5-Dimetil-1-(5-trifluorometil-furan-2-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina,

3-[3,5-Dimetil-1-(5-metil-isoxazol-3-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina,

4-cloro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

[2-(4-metoxi-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

3-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

3-{3,5-Dimetil-1-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetil]-1H-pirazol-4-ilmetil}-1H-pirrolo[2,3-b]piridina,

3-[3,5-Dimetil-1-(4-metil-2-fenil-tiazol-5-ilmetil)-1H-pirazol-4-ilmetil]-1H-pirrolo[2,3-b]piridina,

2-metoxi-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

[2-(2,4-dicloro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

[2-(4-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

[2-(2-fluoro-fenil)-etil]-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

((S)-1-fenil-etil)-amida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

3-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

4-fluoro-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

4-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

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2-metil-bencilamida del ácido 3,5-Dimetil-4-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-pirazol-1-carboxílico,

[2-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico,

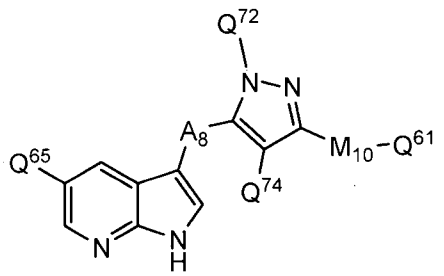
4-fluoro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico,

4-cloro-bencilamida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico,

[(S)-1-(4-fluoro-fenil)-etil]-amida del ácido 4-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-3,5-dimetil-pirazol-1-carboxílico; y

todas las sales, profármacos, tautómeros, o isómeros de los mismos.

9. Un compuesto de conformidad con la Reivindicación **1** que tiene la estructura química de la Fórmula IIg,



todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

A_8 es $-CH_2-$, o $-C(O)-$;

Q^{65} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

M_{10}, Q^{61}, Q^{72}, Q^{74}, y R^{41} son como se define para la Reivindicación 1.

10. El compuesto de conformidad con la Reivindicación **9** seleccionado del grupo que

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consiste de:

[1-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-(4-fluoro-bencil)-amina,

(4-fluoro-bencil)-[1-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-1H-pirazol-3-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina,

(4-fluoro-bencil)-{1-metil-5-[5-(1-metil-1H-pirazol-4-il)-1H-pirrolo[2,3-b]piridin-3-ilmetil]-1H-pirazol-3-il}-amina,

(5-Cloro-1H-pirrolo[2,3-b]piridin-3-il)-[2-etil-5-(4-fluoro-bencilamino)-2H-pirazol-3-il]-metanona,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-etil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina,

3-[5-(4-fluoro-bencilamino)-2-metil-2H-pirazol-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

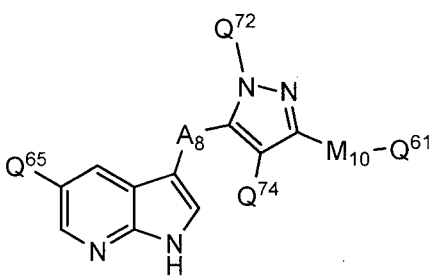
(3-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(2,5-difluoro-bencil)-amina; y

todas las sales, profármacos, tautómeros, o isómeros de los mismos.

11. El compuesto de conformidad con la Reivindicación **9** es [5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-1-metil-1H-pirazol-3-il]-(4-fluoro-bencil)-amina, 3-[5-(4-fluoro-bencilamino)-2-metil-2H-pirazol-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo, o cualquier sales, profármacos, tautómeros, o isómeros de los mismos.

12. Un compuesto de conformidad con la Reivindicación **1** que tiene la estructura química de la Fórmula IIp,



todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

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A_8 es $-CH_2-$, o -C(O)-;

Q^{65} es hidrógeno, -CN, $-OR^{41}$, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo o heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, y $-OR^{41}$; y

M_{10}, Q^{61}, Q^{72}, Q^{74}, y R^{41} son como se define para la Reivindicación 1.

13. El compuesto de conformidad con la Reivindicación **12** seleccionado del grupo que consiste de:

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina,

[4-Etil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina,

(4-fluoro-bencil)-[4-metil-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-3-ilmetil-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-2-ilmetil-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1,5-dimetil-1H-pirazol-3-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-2H-pirazol-3-ilmetil)-amina,

[2-(4-fluoro-bencilamino)-tiazol-5-il]-(1H-pirrolo[2,3-b]piridin-3-il)-metanona,

{2-[(4-Cloro-bencil)-metil-amino]-tiazol-5-il}-(1H-pirrolo[2,3-b]piridin-3-il)-metanona,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-tiazol-2-ilmetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina,

Bencil-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

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[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-metoxi-bencil)-amina,

(4-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-2H-pirazol-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-tiazol-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-metil-tiazol-5-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-cloro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-dimetil-tiazol-5-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-etil-5-metil-3H-imidazol-4-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4,5-dimetil-tiofen-2-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,5-dimetil-tiofen-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina,

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[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-3-ilmetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-cloro-piridin-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1-etil-1H-pirazol-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-cloro-6-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-fenetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-difluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina,

(2-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-cloro-4-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3,5-dicloro-piridin-4-ilmetil)-

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amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-trifluorometil-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina; y

todas las sales, profármacos, tautómeros, o isómeros de los mismos.

14. El compuesto de conformidad con la Reivindicación **12** seleccionado del grupo que consiste de:

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-metoxi-bencil)-amina,

(4-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(4-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metoxi-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-fluoro-piridin-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-tiazol-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-cloro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-3-ilmetil)-amina,

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[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-3-ilmetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-piridin-4-ilmetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(3-cloro-piridin-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(1-etil-1H-pirazol-4-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-fluoro-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(5-metoxi-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-fenetil-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2,4-difluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-fluoro-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metoxi-piridin-3-ilmetil)-amina,

(2-Cloro-bencil)-[4-cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-metil-bencil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(2-cloro-4-fluoro-bencil)-amina,

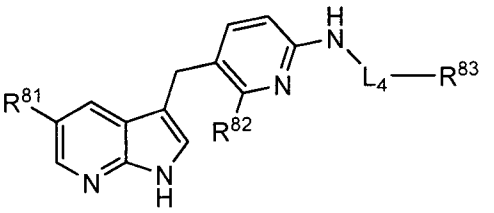
[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-morfolin-4-il-piridin-2-ilmetil)-amina,

[4-Cloro-5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-tiazol-2-il]-(6-metil-piridin-2-ilmetil)-amina; y

todas las sales, profármacos, tautómeros, o isómeros de los mismos.

15. Un compuesto que tiene la estructura química de la Fórmula III,

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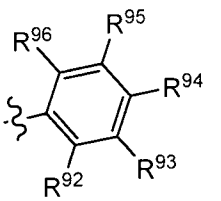
todas las sales, profármacos, tautómeros, e isómeros del mismo,

en donde:

L_4 es $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, $-C(O)-$ o $-C(O)NH-$;

R^{81} se selecciona del grupo que consiste de hidrógeno, $-OR^{41}$, -CN, flúor, cloro, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$;

R^{82} se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-3}, alquilo C_{2-3} sustituido con flúor, OH, alcoxi C_{1-3}, y alcoxi C_{1-3} sustituido con flúor;

R^{83} es heterocicloalquilo, heteroarilo, o  , en el cual  indica el punto de unión de R^{83} a L_4 de la Fórmula III, en donde el heterocicloalquilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$;

R^{92}, R^{93}, R^{94}, R^{95}, y R^{96} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, cicloalquilamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ y $-S(O)_2R^{41}$;

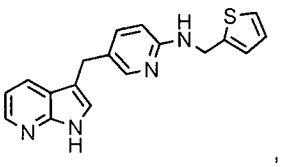
R^{40} se selecciona del grupo que consiste de alquilo inferior, y alquilo inferior sustituido con flúor;

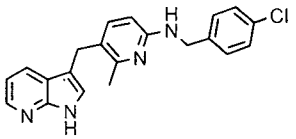
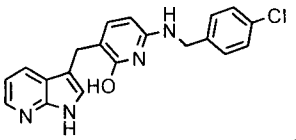
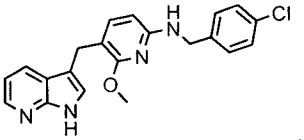
R^{41} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior,

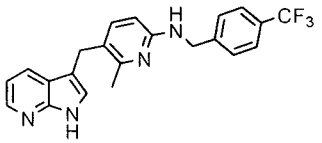
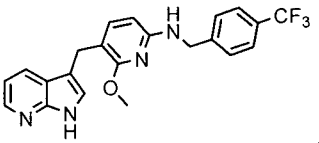
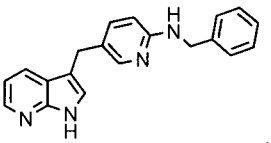
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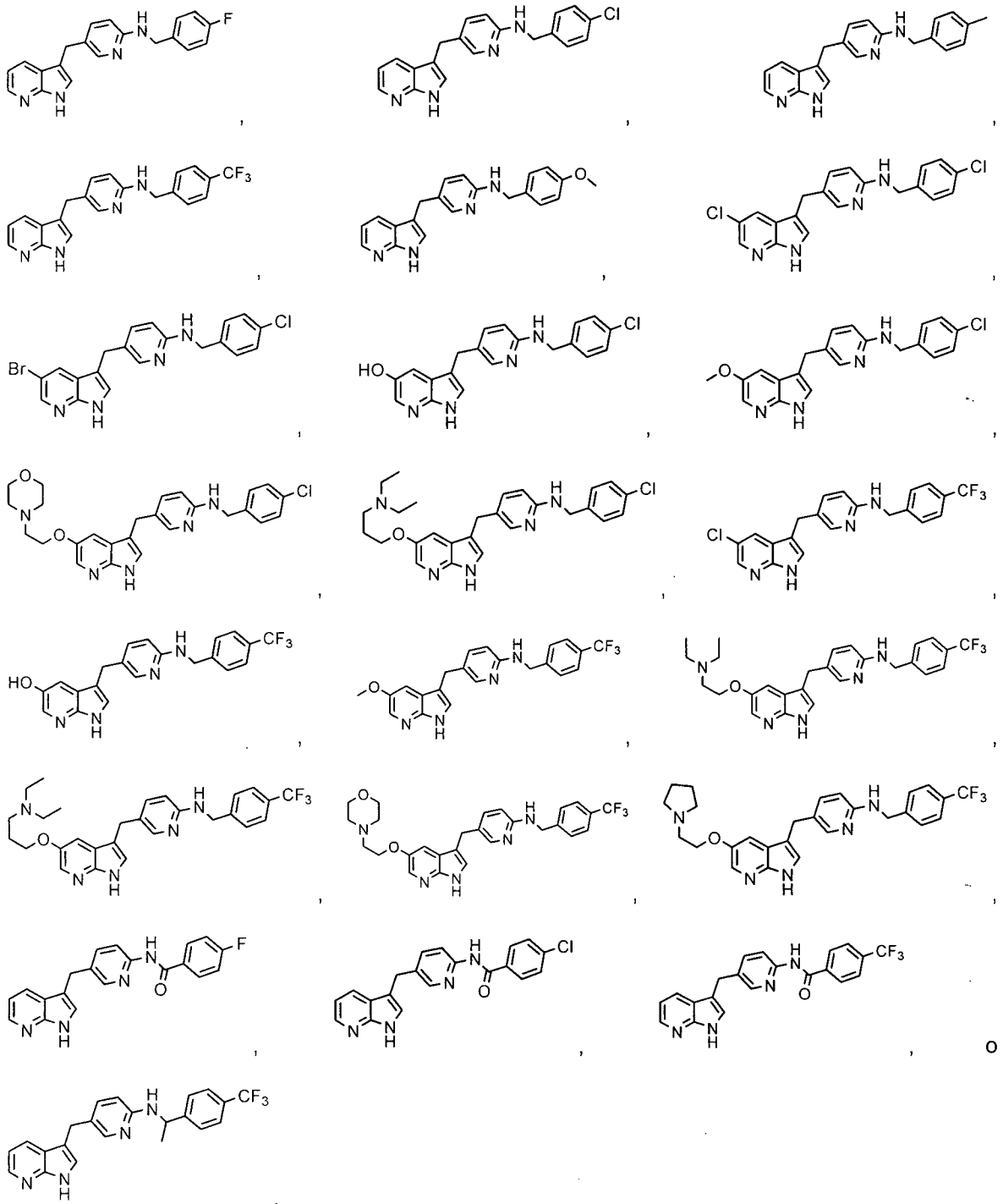
cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, y en donde el cicloalquilo, heterocicloalquilo, arilo, y heteroarilo, como R^{41} o como sustituyentes de alquilo inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halógeno, alquilo inferior, alquilo inferior sustituido con flúor, y cicloalquilamino; y

R^{42} en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, heterocicloalquilo y heteroarilo, en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, mono-alquilamino, di-alquilamino, y cicloalquilamino, y en donde el heterocicloalquilo y heteroarilo se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior y alcoxi inferior sustituido con flúor;

siempre y cuando, sin embargo, el compuesto no sea  ,

 ,  ,  ,

 ,  ,  ,



16. El compuesto de conformidad con la Reivindicación **15** seleccionado del grupo que consiste de:

Piridin-3-ilmetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-Morfolin-4-il-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

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2-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida,

[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido 2,5-Dimetil-2H-pirazol-3-carboxílico,

5-Metil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amida del ácido pirazina-2-carboxílico,

3-Cloro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida,

4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida,

N-[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-3-trifluorometil-benzamida,

3-Cloro-4-fluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida,

3,4-Difluoro-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida,

3-Metoxi-N-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-benzamida,

((R)-1-Fenil-etil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(3-Morfolin-4-il-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[1-(2-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[2-(3-fluoro-fenil)-etil]-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(3-Cloro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-trifluorometil-piridin-3-ilmetil)-amina,

(3-Cloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

Fenetil-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2,4-Difluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-Metil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(6-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-Cloro-4-fluoro-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(5-Metoxi-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

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(3-fluoro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(6-Metoxi-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(4-fluoro-2-trifluorometil-bencil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[5-(1H-Pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina,

(3,5-Dicloro-piridin-4-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(6-Morfolin-4-il-piridin-2-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(5-fluoro-piridin-3-ilmetil)-[5-(1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(3-Cloro-piridin-4-ilmetil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

3-{6-[(3-Cloro-piridin-4-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

3-[6-(4-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

3-[6-(4-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-fluoro-bencil)-amina,

3-[6-(2-fluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

(2-fluoro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

3-{6-[(6-Trifluorometil-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

3-[6-(2-Trifluorometil-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina,

[5-(5-Metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-trifluorometil-bencil)-amina,

3-[6-(2,6-Difluoro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2,6-difluoro-bencil)-amina,

(2-Cloro-bencil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

(2-Cloro-bencil)-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

3-[6-(2-Cloro-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

(6-Metoxi-piridin-3-ilmetil)-[5-(5-metil-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-amina,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(6-metoxi-piridin-3-ilmetil)-amina,

3-{6-[(6-Metoxi-piridin-3-ilmetil)-amino]-piridin-3-ilmetil}-1H-pirrolo[2,3-b]piridina-5-

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carbonitrilo,

[5-(5-Cloro-1H-pirrolo[2,3-b]piridin-3-ilmetil)-piridin-2-il]-(2-metoxi-piridin-3-ilmetil)-amina,

3-[6-(2-Trifluorometoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo,

3-[6-(2-Etoxi-bencilamino)-piridin-3-ilmetil]-1H-pirrolo[2,3-b]piridina-5-carbonitrilo; y

todas las sales, profármacos, tautómeros, o isómeros de los mismos.

17. Una composición que comprende un portador farmacéuticamente aceptable y un compuesto de conformidad con cualquiera de las Reivindicaciones **1-16**.

18. Un método para tratar un sujeto que adolece o está en riesgo de una enfermedad o padecimiento mediado por c-kit y/o c-fms, que comprende administrar al sujeto una cantidad efectiva de un compuesto de conformidad con cualquiera de las Reivindicaciones **1-16**.

19. El método de conformidad con la Reivindicación **18**, en donde la enfermedad o padecimiento se selecciona del grupo que consiste de tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal, glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mieloma múltiple, mastocitosis, melanoma, cáncer de mama, cáncer ovárico, cáncer de próstata, tumores de mastocitos caninos, metástasis de cáncer a hueso u otros tejidos, hipertrofia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, lupus eritematoso sistémico, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica, enfisema, ateroesclerosis, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, lipólisis, hipereosinofilia, osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia,, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, apoplejía, enfermedad de Alzheimer, enfermedad de Parkinson, dolor inflamatorio, dolor crónico, y dolor óseo.

20. El método de conformidad con la Reivindicación **19**, en donde el compuesto se aprueba para su administración a un humano.

21. Un equipo que comprende una composición de conformidad con la Reivindicación

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17.

22. El equipo de conformidad con la Reivindicación **21**, en donde la composición se aprueba para una indicación médica seleccionada del grupo que consiste de tumores de mastocitos, cáncer de pulmón de células pequeñas, cáncer testicular, tumores de estroma gastrointestinal, glioblastoma, astrocitoma, neuroblastoma, carcinomas del tracto genital femenino, sarcomas de origen neuroectodérmico, carcinoma colorectal, carcinoma in situ, neoplasia de células de Schwann asociada con neurofibromatosis, leucemia mieloide aguda, leucemia linfocítica aguda, leucemia mielógena crónica, mieloma múltiple, mastocitosis, melanoma, cáncer de mama, cáncer ovárico, cáncer de próstata, tumores de mastocitos caninos, metástasis de cáncer a hueso u otros tejidos, hipertrofia, asma, artritis reumatoide, rinitis alérgica, esclerosis múltiple, síndrome inflamatorio intestinal, rechazo de transplantes, lupus eritematoso sistémico, colitis ulcerativa, enfermedad de Crohn, enfermedad pulmonar obstructiva crónica, enfisema, ateroesclerosis, Diabetes tipo I, Diabetes tipo II, insensibilidad a insulina, hiperglucemia, lipólisis, hipereosinofilia, osteoporosis, riesgo incrementado de fractura, enfermedad de Paget, hipercalcemia,, glomerulonefritis, nefritis intersticial, nefritis por Lupus, necrosis tubular, nefropatía diabética, apoplejía, enfermedad de Alzheimer, enfermedad de Parkinson, dolor inflamatorio, dolor crónico, y dolor óseo.

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RESUMEN

Compuestos activos sobre las proteína tirosina cinasas receptoras c-kit y/o c-fms se proporcionan con este documento. También se proporcionan con este documento composiciones útiles para el tratamiento de enfermedades o padecimientos mediados por c-kit y/o enfermedades o padecimientos mediados por c-fms, y métodos para el uso de las mismas.

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PATENT COOPERATION TREATY

3805 RECEIVED
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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

D 9/5/08
22mo= 9/22/08

(PCT Rule 44.1)

To:
FOLEY & LARDNER LLP
Attn. Warburg, Richard
11250 El Camino Real, Suite 200
San Diego, CA 92130-2677
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*	05/06/2008
Applicant's or agent's file reference: 039363-4101A	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US2007/085289	International filing date *(day/month/year)*: 20/11/2007
Applicant: PLEXXIKON, INC.	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chantal Gottar

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
039363-4101A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/085289	20/11/2007	22/11/2006
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 6 sheets.

[X] 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:
      [X] 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. [X] **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**,
   [X] 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**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

4A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085289

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/062795 A (PLEXXIKON INC [US]; IBRAHIM PRABHA [US]) 14 July 2005 (2005-07-14) Page 189, 191-193	1,9,12, 17
X	WO 2006/009755 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26) Formula I; paragraphs [0121] - [0132]; claims 1,35; tables 1,2	1-22
X	WO 2006/009797 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26) Formula I, paragraphs [0017] - [0019]; claims 1-20; examples 1-7	15-22

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2008	05/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rudolf, Manfred

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/013896 A (PLEXXIKON INC [US]; ZHANG CHAO [CN]; ZHANG JIAZHONG [CN]; IBRAHIM PRAB) 1 February 2007 (2007-02-01) paragraph [0418]	15-22
P,X	WO 2007/106236 A (SGX PHARMACEUTICALS INC [US]; ARNOLD WILLIAM D [US]; BOUNAUD PIERRE [U) 20 September 2007 (2007-09-20) pages 154,157; claims 1,80	15,17-22

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 54-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 18-20

Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/085289

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. [X] Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

national application No
PCT/US2007/085289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005062795 A	14-07-2005	AU 2004308299 A1	14-07-2005
		CA 2550361 A1	14-07-2005
		EP 1696920 A2	06-09-2006
		JP 2007521334 T	02-08-2007
WO 2006009755 A	26-01-2006	AU 2005265017 A1	26-01-2006
		CA 2570817 A1	26-01-2006
		EP 1755597 A2	28-02-2007
		JP 2008503473 T	07-02-2008
		US 2006058339 A1	16-03-2006
		WO 2006009797 A1	26-01-2006
WO 2006009797 A	26-01-2006	AU 2005265017 A1	26-01-2006
		CA 2570817 A1	26-01-2006
		EP 1755597 A2	28-02-2007
		JP 2008503473 T	07-02-2008
		US 2006058339 A1	16-03-2006
		WO 2006009755 A2	26-01-2006
WO 2007013896 A	01-02-2007	AU 2006272951 A1	01-02-2007
		CA 2608733 A1	01-02-2007
		EP 1885723 A2	13-02-2008
		NO 20075992 B	13-02-2008
		US 2007032519 A1	08-02-2007
WO 2007106236 A	20-09-2007	AR 059620 A1	16-04-2008

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/085289	20.11.2007	22.11.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 A61K31/437

Applicant
PLEXXIKON, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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D-80298 Munich
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Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form PCT/ISA/210

Authorized Officer
Rudolf, Manfred
Telephone No. +49 89 2399-8604

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/085289

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2007/085289

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 18-20 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 18-20 with respect to industrial applicability relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/085289

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-8,10,11,13-16,18-22
	No:	Claims	1,9,12,17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-17,21,22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Re Item III.

Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Re Item V.

1 The following documents are mentioned in the search report:

D1: WO 2005/062795 A (PLEXXIKON INC [US]; IBRAHIM PRABHA [US]) 14 July 2005 (2005-07-14)
D2: WO 2006/009755 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26)
D3: WO 2006/009797 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26)
D4: WO 2007/013896 A (PLEXXIKON INC [US]; ZHANG CHAO [CN]; ZHANG JIAZHONG [CN]; IBRAHIM PRAB) 1 February 2007 (2007-02-01)
D5: WO 2007/106236 A (SGX PHARMACEUTICALS INC [US]; ARNOLD WILLIAM D [US]; BOUNAUD PIERRE [U) 20 September 2007 (2007-09-20)

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,9,12,17 is not new in the sense of Article 33(2) PCT.

Document D1 discloses compounds and compositions which fall within the scope of the abovementioned claims (e.g. D1, page 189).

3. The present application does not meet the criteria of Article 33(1) PCT, because the

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subject-matter of claims 1-22 does not involve an inventive step in the sense of Article 33(3) PCT.

Relevant prior art appear to be documents D2 and D3, both describing compounds useful for treatment of c-kit mediated diseases. Certain compounds specifically disclosed in these documents have been excised from the scope of the present claims by means of provisos. However, the general formulae disclosed in D2 and D3 suggest compounds as now claimed and the use thereof for treatment of c-kit mediated diseases. Insofar the now claimed compounds correspond to those of the general formulae of the c-kit modulators suggested in D2 and D3, these compounds and their use for treating c-kit mediated diseases are obvious.

Re Item VI.

Documents D4 and D5 have been published after the relevant filing date but enjoy earlier priorities. These documents describes compounds which correspond to those mentioned in claim 15.

Re Item VIII.

Certain claims are directed not only to compounds of the formulae cited therein but also extend to "isomers" thereof. It has not been shown in the present application, and it is contrary to common chemical knowledge that the same biological activity can be expected from isomers of the claimed compounds (i.e. compounds having the same molecular formula but having different structure). The claims therefore embrace subject matter which is neither disclosed nor supported by the present application.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 May 2008 (29.05.2008)

PCT

(10) International Publication Number
WO 2008/064255 A3

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/437* (2006.01)

(21) International Application Number:
PCT/US2007/085289

(22) International Filing Date:
20 November 2007 (20.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/860,749 22 November 2006 (22.11.2006) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHANG, Chao** [CN/US]; 397 Springfield Plaza, Moraga, CA 94556 (US). **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). **ARTIS, Dean R.** [US/US]; 50 Arlmont Drive, Kensington, CA 94707 (US). **BREMER, Ryan** [US/US]; 476 Weldon Avenue, Apt. 3, Oakland, CA 94610 (US). **WU, Guoxian** [US/US]; 240 Ventura Avenue, Palo Alto, CA 94306 (US). **ZHU, Hongyao** [US/US]; 91 Bolivar Drive, Suite A, Berkeley, CA 94710 (US). **NESPI, Marika** [IT/US]; 564 San Luis Road, Berkeley, CA 94707 (US).

(74) Agent: **WARBURG, Richard**; Foley & Lardner, 11250 El Camino Real, Suite 200, San Diego, CA 92130 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
14 August 2008

(54) Title: COMPOUNDS MODULATING C-FMS AND/OR C-KIT ACTIVITY AND USES THEREFOR

(57) Abstract: Compounds active on the receptor protein tyrosine kinases c-kit and/or c-fms are provided herewith. Also provided herewith are compositions useful for treatment of c-kit mediated diseases or conditions and/or c-fms-mediated diseases or conditions, and methods for the use thereof.

WO 2008/064255 A3

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085289

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/062795 A (PLEXXIKON INC [US]; IBRAHIM PRABHA [US]) 14 July 2005 (2005-07-14) Page 189, 191-193	1,9,12, 17
X	WO 2006/009755 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26) Formula I; paragraphs [0121] - [0132]; claims 1,35; tables 1,2	1-22
X	WO 2006/009797 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; HURT CLARENCE R [US]; ZHANG) 26 January 2006 (2006-01-26) Formula I, paragraphs [0017] - [0019]; claims 1-20; examples 1-7	15-22

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2008	05/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rudolf, Manfred

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/085289

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/013896 A (PLEXXIKON INC [US]; ZHANG CHAO [CN]; ZHANG JIAZHONG [CN]; IBRAHIM PRAB) 1 February 2007 (2007-02-01) paragraph [0418]	15-22
P,X	WO 2007/106236 A (SGX PHARMACEUTICALS INC [US]; ARNOLD WILLIAM D [US]; BOUNAUD PIERRE [U) 20 September 2007 (2007-09-20) pages 154,157; claims 1,80	15,17-22

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 54-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 18-20

Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/085289

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. [X] Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/085289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005062795 A	14-07-2005	AU 2004308299 A1	14-07-2005
		CA 2550361 A1	14-07-2005
		EP 1696920 A2	06-09-2006
		JP 2007521334 T	02-08-2007
WO 2006009755 A	26-01-2006	AU 2005265017 A1	26-01-2006
		CA 2570817 A1	26-01-2006
		EP 1755597 A2	28-02-2007
		JP 2008503473 T	07-02-2008
		US 2006058339 A1	16-03-2006
		WO 2006009797 A1	26-01-2006
WO 2006009797 A	26-01-2006	AU 2005265017 A1	26-01-2006
		CA 2570817 A1	26-01-2006
		EP 1755597 A2	28-02-2007
		JP 2008503473 T	07-02-2008
		US 2006058339 A1	16-03-2006
		WO 2006009755 A2	26-01-2006
WO 2007013896 A	01-02-2007	AU 2006272951 A1	01-02-2007
		CA 2608733 A1	01-02-2007
		EP 1885723 A2	13-02-2008
		NO 20075992 B	13-02-2008
		US 2007032519 A1	08-02-2007
WO 2007106236 A	20-09-2007	AR 059620 A1	16-04-2008

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de 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 [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-052610- -00000-0000
Fecha: 2009-05-21 16:49:11 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 434

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Bogotá D.C. - Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
PLEXXIKON, INC

REFERENCIA		
	Radicación No.	9 52610
	Solicitud internacional	pct/US2007/085289
	Fecha inicio fase nacional	22/06/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8637

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 31 JUL. 2009
adpa11

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
PLEXXIKON, INC

REFERENCIA		
	Radicación No.	9 52610
	Solicitud internacional	pct/US2007/085289
	Fecha inicio fase nacional	22/06/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8638

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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