

No. 11-058067-00000-0000

Fecha: 2011-05-11 17:17:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYI Eva: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 131

PCT



Industria y Comercio

SUPERINTENDENCIA

11-58067

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

Q.P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENT.

SOLICITUD DE PATENTE DE
INVENCION

TITULO: PIRAZOLILAMINOPIRIDINAS COMO INHIBIDORES DE FAK.

SOLICITANTE: GLAXOSMITHKLINE LLC

DIRECCIÓN: One Franklin, Plaza, 200 North 16th Street Philadelphia,
Pennsylvania 19102, Estados Unidos

APODERADO: CARLOS R. OLARTE

BOGOTÁ 11 de Mayo de 2011

P2011/000087

27-05-2011



OLARTEMOURE

OLARTE MOURE & ASOC

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-058067 - 00000-0000

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Act. 411 PRESENTACION Folios: 131

PETITORIO - FORMULARIO PATENTE PCT

ENTRADA EN FASE NACIONAL

P2011/000087

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: GLAXOSMITHKLINE LLC.

Dirección: One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102.

Nacionalidad o Domicilio: Estados Unidos

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: Diagonal 34 No. 5-28, Bogotá

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ 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/US2009/062163 Fecha Octubre 27, 2009

Publicación Internacional No. WO 2010/062578 Fecha Junio 03, 2010

6

Título (54) PIRAZOLILAMINOPIRIDINAS COMO INHIBIDORES DE FAK.

Clasificación Internacional (51) A61K 31/535.

Prioridad

SI ☒ NO ☐

(33) País de Origen

US

US

US

(32) Fecha

Octubre 27, 2008

Mayo 15, 2009

Septiembre 15, 2009

(31) Número de Solicitud

61/108,568

61/178,517

61/242.432

9

Comprobante de pago No. 11-

Fecha Mayo de 2011

10

ANEXOS

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso. Adjunto copia simple Ver Expediente No. 09-149.371

☒

Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la regla 4.17 (ii) del PCT.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

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. Formulario PCT/IB/306

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-

4

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0044741

Bogotá D.C., Mayo 10 de 2011 - 16:19:06

RECIBIDO DE : OLARTERAISBECK

NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157074481	10/05/2011	10.179.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00	571.000.00
				\$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-058067- -00000-0000

Fecha: 2011-05-11 17:17:02
Tra. 11 PATENTE I/II
Act. 411 PRESENTACIONDep. 2020 DIR. NUEVAS CR
Eva: 378 FASE NACIONAL I
Folios: 131

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C. - Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Mayo 10 de 2011 - 16:19:06

Apostilla adjunta:

APOSTILLA: (Convention de La Haye du 5 octobre 1961)	
1. País:	Estados Unidos de América
<u>El presente documento público</u>	
2. Ha sido firmado por:	Deborah A. Becker
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	Deborah A. Becker, Notario Público del Condado de Montgomery, Mancomunidad de Pensilvania.
<u>Certificado</u>	
5. En:	Harrisburg, Pensilvania.
6. El:	Día 9 de febrero de 2010
7. Por:	Pedro A. Cortés, Secretario de la Mancomunidad de Pensilvania.
8. Bajo el No.:	201003472
9. Sello / estampilla:	Gran sello del Secretario de la Mancomunidad de Pensilvania.
10. Firma:	Por: (Firmado) Pedro A. Cortés

FIN DE LA TRADUCCIÓN

Certificación: Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender. Documento: "Apostilla" Fecha: 25 de febrero de 2010. Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia) Licencia # 376 de 1993, expedida por el Ministerio de Justicia. Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C. Teléfonos: (571) 218 2908, (571) 623 2925. E-mail: lorceres15@yahoo.com Traducción # 14-618	
--	--

Traductor: 
JORGE E. SIERRA
Licencia 376-1993 A

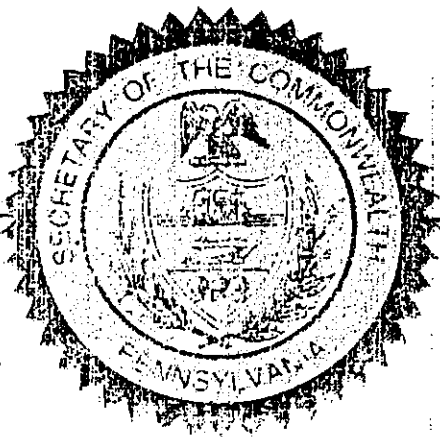
APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : United States of America
2. This public document has been signed by **DEBORAH A BECKER**
3. acting in the capacity of **NOTARY PUBLIC**
4. bears the seal/stamp **DEBORAH A BECKER , NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OF PENNSYLVANIA**
5. at Harrisburg, Pennsylvania
6. The 9th day of February, 2010
7. by Pedro A. Cortés, Secretary of the Commonwealth of Pennsylvania
8. No: 201003472
9. Seal/Stamp
10. Signature

Certified

Pedro A. Cortés

Pedro A. Cortés



Power of Attorney

The undersigned,

domiciled in

One Franklin Plaza, 200 North 16th Street Philadelphia, Pennsylvania 19102
by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck 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, collect refunds, desist, settle, conciliate or negotiate. 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.

Signature/Firma:


Edward R. Gimmi

Date/Fecha: 18 January 2010

City/Country/Ciudad,País: King of Prussia, Pennsylvania, USA

GLAXOSMITHKLINE LLC

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** poder 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, transigir, 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.

Poder

6
Carlos R. Olarte
J. Ian Raisbeck
Juan Guillermo
Moure
Natalia Castro

Alexander Agudelo
Catalina Barbastefano
Ángela Correa
Erika Rico
Carlos A. Parra
Andrés Alvarado
Gina Arias
Juan Felipe Acosta
Andrés Rincón
Grace García
Mariana Franco

Of Counsel
Guillermo Chahín
Graciela Melo
Jacqueline Chaparro

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

18 January 2010

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

709 Swedeland Road, King of Prussia, Pennsylvania, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Authorized Attorney and Signatory of GlaxoSmithKline LLC

3. That GlaxoSmithKline LLC, having its principal place of business located in Philadelphia, Pennsylvania, USA 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):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Edward R. Gimmi

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

3. Que

con sede principal ubicada en

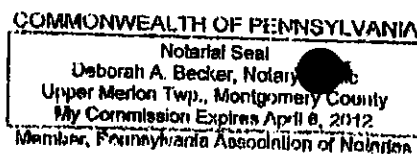
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

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

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):

Deborah A. Becker



Box No. VIII(iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America). The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII(1) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))
for the purposes of the designation of the United States of America:
I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/US2009/062163 filed 27 October 2009 (if furnishing declaration pursuant to Rule 26ter).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Application," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: _____

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. §1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part.

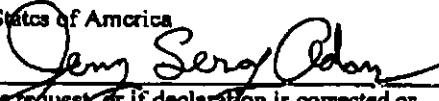
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Jerry Leroy ADAMS

Residence: 1250 South Collegeville Road, Collegeville, PA 19426

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: United States of America

Inventor's Signature: 

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: Dec. 7th 2009

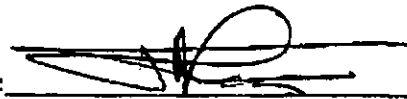
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: Thomas H FAITG

Residence: 1250 South Collegeville Road, Collegeville, PA 19426

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: France

Inventor's Signature: 

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: Dec. 8th 2009

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII(iv)".

8

Continuation of Box No. VIII(i) to (v) Declaration

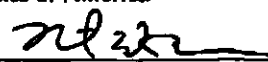
If the space is insufficient in any of Boxes Nos. VIII(i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII " (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name: Neil W JOHNSON

Residence: 1250 South Collegeville Road, Collegeville, PA 19426

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: United States of America

Inventor's Signature: 
(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: Dec 8, 2009
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: Hong LIN

Residence: 1250 South Collegeville Road, Collegeville, PA 19426

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: China

Inventor's Signature: 
(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: Dec. 8, 2009
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Box No. VIII(iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY
The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII(i) to (v) (in general) and the specific Notes to Box No. VIII(iii) and 51*bis*.1(a)(iii)

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

in relation to International Application No. PCT/US2009/

SMITHKLINE BEECHAM CORPORATION is entitled to claim priority of earlier application No. 61/108568 filed 27 October 2008; 61/178517 filed 15 May 2009 and 61/242432 filed 15 September 2009 in the United States of America by virtue of the following:

an assignment from Jerry Leroy ADAMS of 1250 South Collegeville Road, Collegeville, PA 19426 to SmithKline Beecham Corporation dated 7 December 2009

an assignment from Thomas H FAITG of 1250 South Collegeville Road, Collegeville, PA 19426 to SmithKline Beecham Corporation dated 8 December 2009

an assignment from Neil W JOHNSON of 1250 South Collegeville Road, Collegeville, PA 19426 to SmithKline Beecham Corporation dated 8 December 2009

an assignment from Hong LIN of 1250 South Collegeville Road, Collegeville, PA 19426 to SmithKline Beecham Corporation dated 8 December 2009

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(iii)".

Form PCT/RO/101 (declaration sheet (iii)) (March 2001; reprint January 2003)

See Notes to the request form

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2010 (03.06.2010)



(10) International Publication Number
WO 2010/062578 A1

(51) International Patent Classification:
A61K 31/535 (2006.01)

(21) International Application Number:
PCT/US2009/062163

(22) International Filing Date:
27 October 2009 (27.10.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/108,568 27 October 2008 (27.10.2008) US
61/178,517 15 May 2009 (15.05.2009) US
61/242,432 15 September 2009 (15.09.2009) US

(71) Applicant (for all designated States except US): **GLAXOSMITHKLINE LLC** [US/US]; One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ADAMS, Jerry, Leroy** [US/GB]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **FAITG, Thomas, H.** [FR/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **JOHNSON, Neil, W.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **LIN, Hong** [CN/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(74) Agents: **KANAGY, James, M.**, et al.; **GLAXOSMITHKLINE**, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King Of Prussia, PA 19406-0939 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

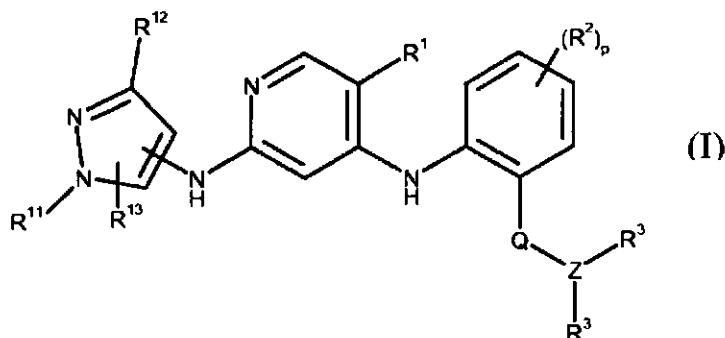
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: **PYRAZOLYLAMINOPYRIDINES AS INHIBITORS OF FAK**



(57) Abstract: The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R¹¹, R¹², R¹³, Q, Z, and p are as described herein. Compounds of the present invention are useful for the treatment of cancers.

PYRAZOLYLAMINOPYRIDINES AS INHIBITORS OF FAK

AREA OF THE INVENTION

This invention relates to a class of pyrazolylaminopyridines that inhibit Focal Adhesion Kinase (FAK), as well as compositions thereof. Compounds of the present invention are useful in the treatment of proliferative diseases including, but not limited to cancer.

BACKGROUND OF THE INVENTION

Tyrosine kinases play an important role in the regulation of many cell processes including cell proliferation, cell survival, and cell migration. It is known that certain tyrosine kinases become activated by mutation or are abnormally expressed in many human cancers. For example, the epidermal growth factor receptor (EGFR) is found mutated and/or overexpressed in breast, lung, brain, squamous cell, gastric, and other human cancers. Selective inhibitors of the tyrosine kinase activity of EGFR have been shown to be of clinical value in treatment of cancers with mutated and/or overexpressed EGFR. Thus, selective inhibitors of particular tyrosine kinases are useful in the treatment of proliferative diseases such as cancer.

FAK (encoded by the gene PTK2) is a non-receptor tyrosine kinase that integrates signals from integrins and growth factor receptors. FAK has been reported to play a role in the regulation of cell survival, growth, adhesion, migration, and invasion (McLean et al 2005, Nat Rev Cancer 5:505-515). Furthermore, FAK is regulated and activated by phosphorylation on multiple tyrosine residues. Overexpression of FAK mRNA and/or protein has been documented in many solid human tumors, including but not limited to, cancers of the breast, colon, thyroid, lung, ovary, and prostate; but also including cancers of hematological origin, including but not limited to leukemia such as acute myeloid leukemia (AML). (Owens et al. 1995, Cancer Research 55: 2752-2755; Agochiya et al. 1999, Oncogene 18: 5646-5653; Gabarro-Niecko et al. 2003, Cancer Metastasis Rev. 22:359-374; Recher et al. 2004, Cancer Research 64:3191-3197; Zhao and Guan, 28:35-49, 2009, Cancer Metastasis Rev.). More significantly, there is evidence that phosphorylated FAK is increased in malignant compared to normal tissues (Grisaru-Granovsky et al. 2005, Int. J. Cancer 113: 372-378) and could represent a prognostic marker of metastasis. FAK activity is clearly implicated in advanced and metastatic human cancer (Zhao and Guan, 28:35-49, 2009, Cancer Metastasis Rev.).

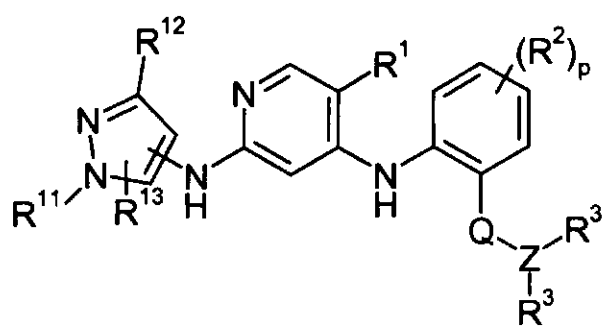
Elimination of FAK by RNAi or expression of a FAK dominant negative has been shown to induce loss of adhesion and cell death in human breast and melanoma cell lines, and to augment docetaxel-mediated apoptosis in ovarian cancer cells (Beviglia et al 2003, Biochem J. 373:201-210, Smith et al 2005, Melanoma Res. 15:357-362, Halder et al 2005, Clin. Cancer Res. 11:8829-8836). However, inhibition of FAK in normal human fibroblasts or immortalized mammary cells

(MCF10A) was found not to cause loss of attachment or apoptosis (Xu et al. 1996 Cell Growth and Diff 7:413-418). Inhibition of FAK by dominant negative expression has also been shown to reduce tumor growth and eliminate lung metastasis of mammary adenocarcinoma cells in a syngeneic rat model (van Nimwegen et al 2005, Cancer Res. 65:4698-4706). Similarly, inhibition of FAK by shRNA inhibited lung metastasis and reduced lethality by 40% in a syngeneic mouse model (Mitra et al 2006, Oncogene 25: 4429-4440). In this study, transient re-expression of wild-type, but not kinase-dead FAK, reversed the shRNA phenotypes. Inhibition of FAK by dominant negative expression in mouse 4T1 carcinoma cells reduced tumor growth and angiogenesis in mice (Mitra et al 2006, Oncogene 25:5969-5984). Furthermore, loss of FAK catalytic activity (reconstitution of FAK-/- cells with kinase-dead FAK) reduced growth of v-Src tumors in mice and decreased angiogenesis.

Thus, there is strong evidence to suggest that inhibition of FAK activity induces apoptosis, loss of adhesion, inhibition of cell growth and migration, and that such inhibition reduces angiogenesis. Accordingly, compounds that inhibit FAK activity would be useful for the treatment of cancer.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula (I):



(I)

or a salt thereof, wherein:

- R¹ is halo, CF₃, C₁-C₆-alkyl, isopropenyl, (C₂-C₆-alkylene) C₃-C₆-cycloalkyl, C₁-C₆-alkoxy, or cyano;
- in R² when p is other than 0, each R² is independently F, Cl, CF₃, methyl, methoxy, CH₂CF₃, -(X)_q-C₁-C₄-alkylene-R⁴, -(X-C₁-C₄-alkylene)_q-NR⁵-C(O)-R⁶, -(X-C₁-C₄-alkylene)_q-(NR⁵)_q-SO_x-R⁷, -(X-C₁-C₄-alkylene)_q-Y-N(R⁸)₂; a 5- to 6-membered heterocycloalkyl-(R⁹)_q group, or a 5- to 6-membered heteroaryl-(R¹⁰)_r group;
- R³ is independently H, C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylene-R⁴, O-C₁-C₆-alkylene-R⁴, or, the R³ groups, together with Z, form a 5- to 6-

- membered cyclic ring optionally substituted with methyl, C₁-C₄-alkylene-R⁴, or C₃-C₆-cycloalkyl;
- R⁴ is H, -(Q)_q-N(R⁸)₂, OH, SH, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, or a 5- to 6-membered heterocycloalkyl-(R⁹)_q group;
- 5 R⁵ is H or C₁-C₆-alkyl;
- R⁶ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, N(R⁸)₂, or a 5- to 6-membered heteroaryl-(R¹⁰)_r group;
- R⁷ is C₁-C₆-alkyl, phenyl-(R⁹)_q, or 5- to 6-membered heteroaryl-(R¹⁰)_r;
- R⁸ is independently H, C₁-C₆-alkyl, -O-C₁-C₆-alkyl or, together with the nitrogen
- 10 atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group;
- R⁹ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, -(Q)_q-N(R⁸)₂, -Q-C₁-C₆-alkyl, -C₁-C₆-alkyl-R⁴, or 5- to 6-membered heterocycloalkyl;
- R¹⁰ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, or -Q-C₂-C₆-alkyl;
- R¹¹ is C₁-C₆-alkyl, CF₃, -CH₂CF₃, -(Q)_q-C₁-C₄-alkylene-R⁴, -Q-N(R⁸)₂, phenyl-
- 15 (R⁵)_s, a 5- to 6-membered heterocycloalkyl-(R⁹)_q group, or a 5- to 6-membered heteroaryl-(R¹⁰)_r group;
- R¹² is H, C₁-C₆-alkyl, F, Cl, CF₃, OH, CN, nitro, COOH, -COO-C₁-C₆-alkyl, -Y-N(R⁸)₂, C₃-C₆-cycloalkyl-R¹⁴, -(X)_q-C₁-C₆-alkylene-R⁴, -(X-C₁-C₆-alkylene)_q-NR⁵-C(O)-R⁶, -(X-C₁-C₆-alkylene)_q-(NR⁵)_q-SO_x-R⁷,
- 20 -(X-C₁-C₆-alkylene)_q-Y-N(R⁸)₂, heterocycloalkyl-(R⁹)_q, heteroaryl-(R¹⁰)_r, or phenyl-(R¹⁵)_s;
- R¹³ is H, F, Cl, C₁-C₆-alkyl, or C₃-C₆-cycloalkyl; or R¹² and R¹³, together with the carbon atoms to which they are attached, form a fused 5- or 6-membered carbocycloalkyl or heterocycloralkyl group;
- R¹⁴ is independently H, C₁-C₆-alkyl, -NR⁵-SO₂-R⁷, -Y-N(R⁸)₂, or
- 25 -(X)_q-C₁-C₆-alkylene-R⁴;
- R¹⁵ is independently F, Cl, CF₃, C₁-C₃-alkyl, or C₁-C₃-alkoxy;
- p is 0, 1, 2, or 3;
- q is 0 or 1;
- r is 0, 1, or 2;
- 30 s is 0, 1, 2, or 3;
- x is 1 or 2;
- Q is -C(O)-, -S(O)-, or -SO₂-;
- X is NR⁵, O, S, -S(O)-, or -SO₂-;

Y is a bond, SO₂, or C(O); and
Z is N or CR⁵.

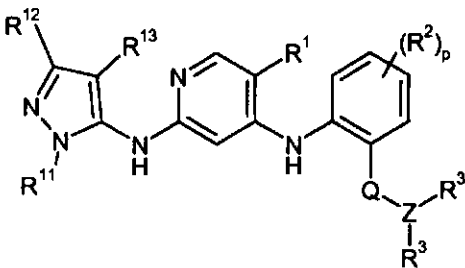
In a further embodiment, the present invention relates to a composition comprising a) the compound of formula (I) or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable excipient.

In a further embodiment, the present invention relates to a method of treating a proliferative disease such as cancer or an abnormal angiogenesis disease such as macular degeneration, comprising administering to a patient in need thereof a pharmaceutically effective amount of the compound of formula (I).

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DETAILED DESCRIPTION OF THE INVENTION

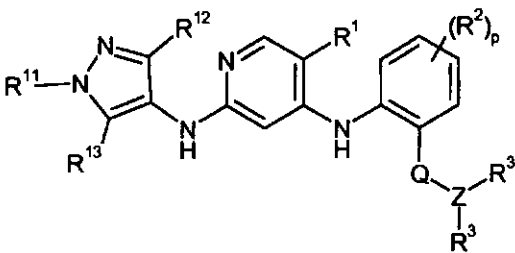
In another aspect, the present invention relates to compounds of formula (Ia):



(Ia)

15 wherein the various groups are the same as set out above for formula (I); or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention is represented by a compound of formula (Ib):



(Ib)

20 wherein the various groups are the same as set out above for formula (I); or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention, Q is C(O) and Z is N.

In another aspect of the present invention, R¹ is Cl, CF₃, or CN;

In another aspect of the present invention, R² is F;

25 In another aspect of the present invention, one R³ is methyl and the other R³ is H;

In another aspect of the present invention, one R³ is methoxy and the other R³ is H;

In another aspect of the present invention, R¹¹ is C₁-C₆-alkyl;

In another aspect of the present invention, R¹² is C₁-C₆-alkyl, hydroxymethyl, or cyclopropyl;

In another aspect of the present invention, R¹³ is H;

5 In another aspect of the present invention, p is 0 or 1;

As used herein, "halo" refers to fluoro, chloro, or bromo.

"C₁-C₆-alkyl" refers to a linear or branched alkyl group including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, *n*-pentyl, and *n*-hexyl.

10 "C₁-C₆-alkoxy" refers to C₁-C₆-alkyl-O- groups, including methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, and *n*-butoxy groups.

The term "alkylene" (e.g., C₂-C₄-alkylene or C₁-C₆-alkylene) refers to a linear or branched hydrocarbon radical having the specified number of carbon atoms. The group "-alkylene-R⁴" refers to a substituted or unsubstituted alkyl group having the specified number of carbon atoms; thus, where R⁴ is H, "alkylene" is synonymous with "alkyl"; otherwise, alkylene is a bivalent
15 radical. Examples of -(X)_q-C₂-C₄-alkylene-R⁴ include -CH₂CH₂-N(CH₃)₂, -CH₂CH₂-OH, -CH₂CH(CH₃)-OCH₃, -N(CH₃)-CH₂CH₂CH₂-piperidinyl; -O-CH₂CH(CH₃)-OCH₃; and the like.

C₃-C₆-cycloalkyl refers to a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl group.

As used herein, "5- or 6-membered heterocycloalkyl" refers to a 5- or 6-membered cycloaliphatic group that includes an O, N, or S heteroatom or a combination thereof. Examples of
20 suitable heterocycloalkyl groups include pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, oxopiperazinyl, morpholino, and thiomorpholino groups.

The R⁸ groups may, together with the nitrogen atom to which they are attached, form a 5- to 6-membered cyclic ring, examples of which include pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, oxopiperazinyl, morpholino, and thiomorpholino groups.

25 The term "heteroaryl" refers to a 5- or 6-membered aromatic group containing at least one N, O, or S atom. Examples of suitable heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, furazanyl, oxazolyl, thiazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, and isothiazolyl.

As used herein, "pharmaceutically acceptable" refers to those compounds, materials,
30 compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication.

The skilled artisan will appreciate that pharmaceutically acceptable salts of compounds of formula (I) may be prepared. More particularly, inasmuch as compounds according to formula (I)
35 contain a basic functional group - and may include an acid functional group - they are capable of forming pharmaceutically acceptable salts by treatment with a suitable acid or base. Suitable acids

include pharmaceutically acceptable inorganic acids and organic acids. Representative pharmaceutically acceptable acids include hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, sulfonic acid, phosphoric acid, acetic acid, hydroxyacetic acid, phenylacetic acid, propionic acid, butyric acid, valeric acid, maleic acid, acrylic acid, fumaric acid, malic acid, malonic acid, tartaric acid, citric acid, salicylic acid, benzoic acid, tannic acid, formic acid, stearic acid, lactic acid, ascorbic acid, *p*-toluenesulfonic acid, oleic acid, and lauric acid.

Suitable bases include inorganic bases, such as hydrides, hydroxides and carbonates of lithium, sodium, potassium, calcium, magnesium, and zinc, as well as organic bases such as arginine, choline, diethylenetriamine, dimethylamine, ethylenediamine, imidazole, lysine, morpholine, proline, and trimethylamine.

As used herein, the term "a compound of formula (I)" or "the compound of formula (I)" refers to one or more compounds according to formula (I). The compound of formula (I) may exist in a crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. The incorporated solvent molecules may be water molecules or non-aqueous such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate molecules. Crystalline lattice incorporated with water molecules are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The present invention includes all such solvates.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. The compounds claimed below include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), or claimed below, as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the claimed compounds as mixtures with isomers thereof in which one or more chiral centers are inverted.

Where there are different isomeric forms they may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

While it is possible that, for use in therapy, a compound of formula (I), as well as salts, solvates and the like, may be administered as a neat preparation, i.e. no additional carrier, the more usual practice is to present the active ingredient confected with a carrier or diluent. Accordingly, the invention further provides pharmaceutical compositions, which includes a compound of formula (I) and salts, solvates and the like, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and salts, solvates, etc, are as described

above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I), or salts, solvates etc, with one or more pharmaceutically acceptable carriers, diluents or excipients.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties" may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Preferred prodrugs for compounds of the invention include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 3500mg, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association a compound of formula (I) with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-

aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

5 Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

10 Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

15 Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or
20 polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and
25 compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that
30 a given quantity contains a predetermined amount of a compound of formula (I). Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as
35 peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit pharmaceutical compositions for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-
5 aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The pharmaceutical compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition
10 requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the intended recipient, the
15 precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, an effective amount of a compound of formula (I) for the treatment of cancer will generally be in the range of 0.001 to 100 mg/kg body weight of recipient per day, suitably in the range of .01 to 10 mg/kg body weight per day. For a 70kg adult the actual amount
20 per day would suitably be from 7 to 700 mg and this amount may be given in a single dose per day or in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, etc., may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

25 Treatments

The compounds and compositions of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer, autoimmune disease, fungal disorders, arthritis, graft
30 rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper or hypo proliferation state (abnormal state) and still requires treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation enhancement may be desired. Thus, in one embodiment, the invention herein includes application to cells or individuals afflicted or impending affliction with any one of these disorders or states.
35 These compounds may also be used for treating macular degeneration associated with neovascularization, such as AMD

The compositions and methods provided herein are particularly deemed useful for the treatment of cancer including tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. They are particularly useful in treating metastatic or malignant tumors. More particularly, cancers that may be treated by the compositions and methods of the invention include,

5 but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat:

Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell,

10 undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma,

15 lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal

20 carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple

25 myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma,

30 sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial

35 carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one or related of the above identified conditions.

In comparison to related 2,4-diaminopyridine derivatives described elsewhere, the compounds of the present invention contain a hydroxamic acid ester function on the 4-aminophenyl ring at the 2-position and an aminopyrazole at 2-position on the pyridine ring. The hydroxamic acid ester function on the phenyl ring, as compared with the corresponding amide, increases potency against FAK on the order of 2-5 fold, particularly *in vitro*, and improves selectivity for FAK over other enzymes. The pyrazole reduces reactivity in the cytochrome P450s. Hence the combination of the hydroxamic acid ester construct on the phenyl ring with an aminopyrazole at 2 position on the pyridine ring provides compounds with enhanced safety and efficacy over other FAK inhibitors such as the 2,4-diaminopyridine derivatives.

The instant compounds can be combined with or co-administered with other therapeutic agents, particularly agents that may enhance the activity or time of disposition of the compounds. Combination therapies according to the invention comprise the administration of at least one compound of the invention and the use of at least one other treatment method. In one embodiment, combination therapies according to the invention comprise the administration of at least one compound of the invention and surgical therapy. In one embodiment, combination therapies according to the invention comprise the administration of at least one compound of the invention and radiotherapy. In one embodiment, combination therapies according to the invention comprise the administration of at least one compound of the invention and at least one supportive care agent (e.g., at least one anti-emetic agent). In one embodiment, combination therapies according to the present invention comprise the administration of at least one compound of the invention and at least one other chemotherapeutic agent. In one particular embodiment, the invention comprises the administration of at least one compound of the invention and at least one anti-neoplastic agent. In yet another embodiment, the invention comprises a therapeutic regimen where the FAK inhibitors of this disclosure are not in and of themselves active or significantly active, but when combined with another therapy, which may or may not be active as a stand alone therapy, the combination provides a useful therapeutic outcome.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an FAK inhibiting compound, as described herein, and a further active ingredient or ingredients, known to

be useful in the treatment of cancer, including chemotherapy and radiation treatment. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer. Preferably, if the administration is not simultaneous, the compounds
5 are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of specified cancers in the present invention.
10 Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-
15 microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and
20 hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Typically, any chemotherapeutic agent that has activity against a susceptible neoplasm being treated may be utilized in combination with the compounds the invention, provided that the
25 particular agent is clinically compatible with therapy employing a compound of the invention. Typical anti-neoplastic agents useful in the present invention include, but are not limited to: alkylating agents, anti-metabolites, antitumor antibiotics, antimetabolic agents, topoisomerase I and II inhibitors, hormones and hormonal analogues; retinoids, signal transduction pathway inhibitors including inhibitors of cell growth or growth factor function, angiogenesis inhibitors, and
30 serine/threonine or other kinase inhibitors; cyclin dependent kinase inhibitors; antisense therapies and immunotherapeutic agents, including monoclonals, vaccines or other biological agents.

Signal transduction pathway inhibitors are those inhibitors which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation or survival. Signal transduction pathway inhibitors useful in the
35 present invention include, but are not limited to, inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphatidyl

inositol-3-OH kinases, myoinositol signaling, and Ras oncogenes. Signal transduction pathway inhibitors may be employed in combination with the compounds of the invention in the compositions and methods described above.

Receptor kinase angiogenesis inhibitors may also find use in the present invention.

- 5 Inhibitors of angiogenesis related to VEGFR and TIE-2 are discussed above in regard to signal transduction inhibitors (both are receptor tyrosine kinases). Other inhibitors may be used in combination with the compounds of the invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($\alpha_v\beta_3$) that inhibit angiogenesis; endostatin and angiostatin (non-RTK)
- 10 may also prove useful in combination with the compounds of the invention. One example of a VEGFR antibody is bevacizumab (AVASTIN®).

- Several inhibitors of growth factor receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors, anti-sense oligonucleotides and aptamers. Any of these growth factor receptor inhibitors may be employed in combination with the compounds of
- 15 the invention in any of the compositions and methods/uses described herein. Trastuzumab (Herceptin®) is an example of an anti-erbB2 antibody inhibitor of growth factor function. One example of an anti-erbB1 antibody inhibitor of growth factor function is cetuximab (Erbix™, C225). Bevacizumab (Avastin®) is an example of a monoclonal antibody directed against VEGFR. Examples of small molecule inhibitors of epidermal growth factor receptors include but
- 20 are not limited to lapatinib (Tykerb™) and erlotinib (TARCEVA®). Imatinib mesylate (GLEEVEC®) is one example of a PDGFR inhibitor. Examples of VEGFR inhibitors include pazopanib, ZD6474, AZD2171, PTK787, sunitinib and sorafenib. Pazopanib and the compounds of formula I and their salts are of particular interest.

- Anti-microtubule or anti-mitotic agents are phase specific agents active against the
- 25 microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

- Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G₂/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β -tubulin subunit of the microtubules, by binding with this protein. Disassembly of
- 30 the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

- Paclitaxel, 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable
- 35 solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by

Wani et al. J. Am. Chem. Soc., 93:2325. 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl. Acad. Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol. Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I. Kingston *et al.*, Studies in Organic Chemistry vol. 26, entitled "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and Medicine, 64:583, 1991; McGuire et al., Ann. Intern. Med., 111:273, 1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797, 1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE[®]. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincalukoblastine sulfate, is commercially available as VELBAN[®] as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincalureblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN[®] as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosuppression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincalureblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE[®]), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL[®] as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN[®] as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN[®]. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia,

nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN[®]. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN[®] tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN[®] TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU[®]. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome[®]. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN[®]. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis)-8-acetyl-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione

hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME[®] or as an injectable as CERUBIDINE[®]. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

5 Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX[®] or ADRIAMYCIN RDF[®].

Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and
10 lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE[®]. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the
15 most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G₂ phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The
20 strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene- β -D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID[®] and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with
25 other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-thenylidene- β -D-glucopyranoside], is commercially available as an injectable solution as VUMON[®] and is
30 commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S
35 phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or

pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mercaptopurine, thioguanine, and gemcitabine.

5 5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis
10 are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

 Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal
15 incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

 Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available
20 as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

25 Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose
30 limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

 Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and
35 by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in

combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

5 Methotrexate, N-[4[[[(2,4-diamino-6-pteridiny) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dihydrofolate reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other
10 chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

 Camptothecins, including, camptothecin and camptothecin derivatives are available or
15 under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

 Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-
20 1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

 Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or
25 SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

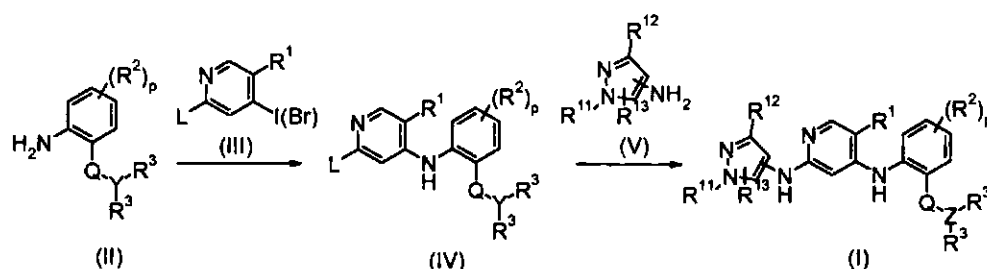
 Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is
30 commercially available as the injectable solution Hycamtin®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of single strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression,
35 primarily neutropenia.

The following schemes illustrate how compounds of the present invention can be prepared. The specific solvents and reaction conditions referred to are also illustrative and are not intended to be limiting.

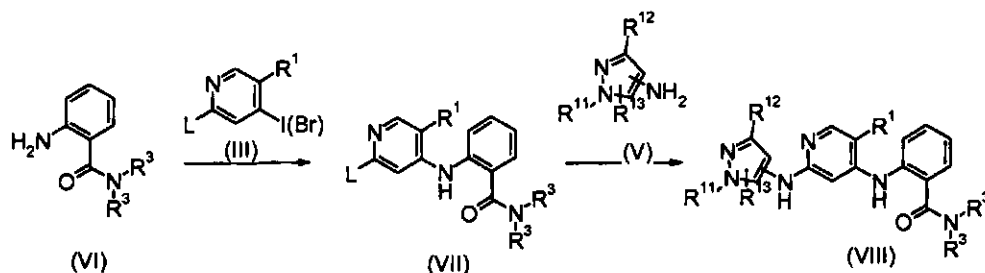
Schemes

- 5 Compounds of formula (I) may be prepared by the methods outlined in Scheme 1 below. Compounds of formula (II) and (III) are commercially available or may be synthesized using techniques conventional in the art. The L group for compound (III) represents a leaving group such as F or Cl. The compounds of formula (II) and (III) may be reacted under reflux or microwave conditions to afford intermediate (IV). The addition reaction is typically done using a
- 10 polar, protic solvents such as *n*-butanol or iso-propanol. Alternatively, metal catalyzed coupling reaction conditions may be used. When compound (II) includes a functional group in need of protection, for example, a hydroxyl or amino group, an appropriate protecting group is advantageously used. Compounds of formula (IV) may then be reacted with an aminopyrazole
- 15 (V), which is commercially available or which may be synthesized using techniques conventional in the art, to afford a compound of formula (I). The reaction is typically carried out in the presence of a metal catalyst, such as a palladium salt, along with an appropriate phosphine ligand. Alternatively, the reaction can be carried out with a catalytic amount of an acid such as hydrochloric or trifluoroacetic acid and in a suitable solvent such as water, 1,4-dioxane, or iso-propanol or a combination thereof; the reaction is advantageously carried out at an advanced
- 20 temperature, for example, under refluxing conditions, or by using a microwave apparatus. The acid catalyst is typically present in an amount of 10-30 mol% with respect to the compound of formula (I).

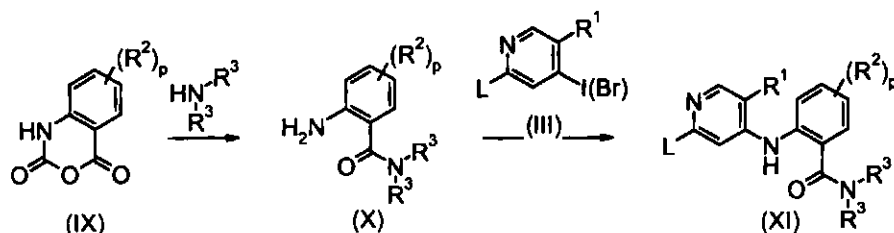
Scheme 1



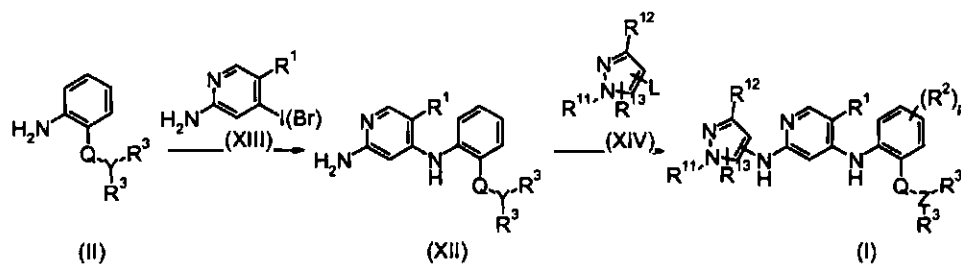
- 25 Compounds of formula (VIII) may be conveniently prepared by the methods outlined in Scheme 1, but starting with an appropriate anthranilamide (VI), as outlined in Scheme 2.

Scheme 2

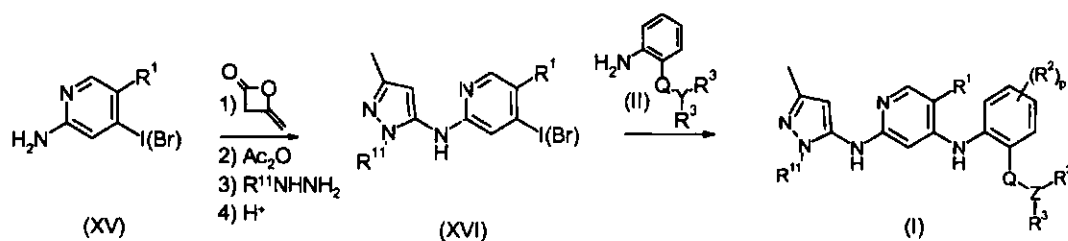
- Compound (VI) may contain additional substituents. For example, as shown in Scheme 3, benzoxazine (IX), which is either commercially available or synthesized using techniques conventional in the art, can be ring-opened with an amine to form benzamide (X), which can then undergo addition with compound (III) to yield the compound of formula (XI).

Scheme 3

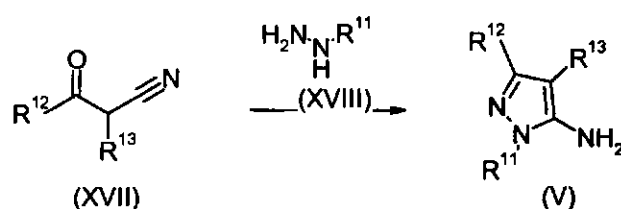
- A compound of formula (XII) may be prepared by reacting a compound of formula (II) with a compound of formula (XIII). This reaction can be carried out as described in Scheme 1. Compounds of formula (XII) may then be reacted with a compound of formula (XIV) to give compounds of formula (I). The reaction may be carried out in inert solvent, in the presence of a metal catalyst and appropriate ligand.

Scheme 4

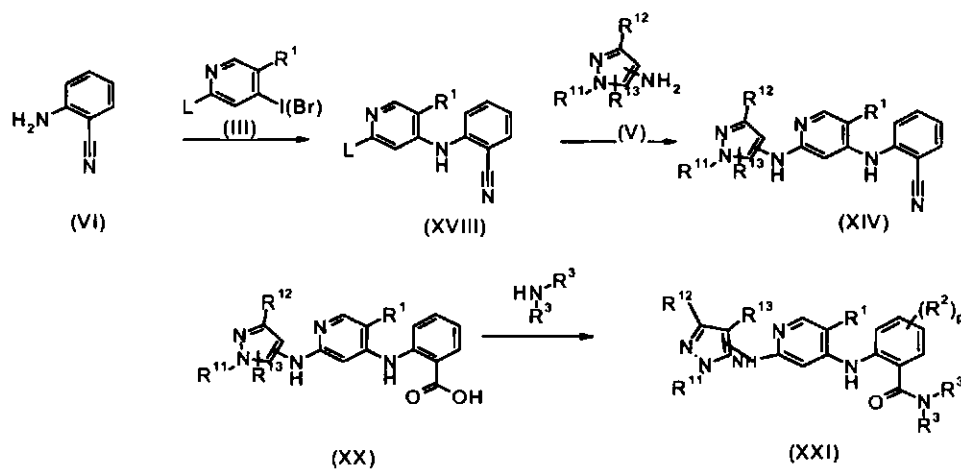
- Certain compounds of formula (I) can also be prepared as outlined in Scheme 5. The amino group of the compound of formula (XV) can first be reacted with diketene followed by acylation and treatment with a hydrazine. Compound of formula (XVI) can then be obtained by treatment with acid, then reacted with a compound of formula (II) to give a compound of formula (I). This last reaction can be carried out as described in Scheme 1.

Scheme 5

- Compounds of formula (V) can be made by the condensation of a substituted hydrazine (XVIII) with the appropriate cyano-ketone (XVII), for example, according to the procedures of
- 5 Honma, T. *et al. J. Med. Chem.* **2002**, Vol. 44 (26), 4628-4640 or Adachi, I. *et al. Chemical & Pharmaceutical Bulletin* **1987**, 35(8), 3235-52 as outlined in Scheme 6.

Scheme 610 Scheme 7

A compound of formula (XXI) can also be prepared as outlined in Scheme 7. The nitrile of formula (XIV) can be hydrolyzed to a carboxylic acid of formula (XX) and then coupled with an amine to give compounds of formula (XXI).



15

EXPERIMENTALSBiochemical assay for FAK activity

Assay 1: GST-tagged (glutathione S-transferase-tagged) FAK was purchased from Invitrogen (PV3832) (www.invitrogen.com). The activity of FAK was measured by monitoring

the phosphorylation of a peptide substrate (Ac-RRRRRRSETDDYAEIID-NH₂; (SEQ ID NO: 1) i.e. Ac-Arg-Arg-Arg-Arg-Arg-Ser-Glu-Thr-Asp-Asp-Tyr-Ala-Glu-Ile-Ile-Asp-NH₂) in the presence of a radio-labeled ATP. To measure inhibitors of FAK, compounds were first prepared as a 10× stock in 10% DMSO. A small portion of each solution (4 μL) was added to a 96-well plate (Corning, 3884). A 6-nM GST-FAK solution was prepared in 1.1× reaction buffer containing 44 mM HEPES, pH=7.2, 11 mM MgCl₂, 2.2 mM MnCl₂, 1.1 mM DTT and 0.011% Tween-20. Then, 20 μL of the 6 nM GST-FAK solution were pre-incubated with the compounds for 30 min at room temperature. The reaction was initiated by adding 16 μL of substrates (62.5 μM peptide, 5 μM ATP and ~0.02 mCi/mL ³³P-γ-ATP) prepared in the above reaction buffer. The reaction was allowed to proceed for 90 min before being quenched with 40 μL of 1% H₃PO₄. A portion of the reaction mixture (60 μL) was transferred to a phospho-cellulose filter plate (Millipore; www.millipore.com, MAPHNOB50) and incubated for 20 minutes. The plate was filtrated, washed three times using 150 μL of 0.5% H₃PO₄ and dried at 50° C for 30 min. After the addition of 60 μL Microscint-20 to the plate, radioactivity was measured using a TopCount (PerkinElmer; www.PerkinElmer.com).

Assay 2: Flag-His-TEV-FAK1 was prepared in-house. Full length Human FAK was expressed using baculovirus in Sf9 cells with N-terminal FLAG-6xHis tags followed by a TEV cleavage site (FLAG-6xHis-TEV-huFAK). The activity of FAK was measured by monitoring the phosphorylation of LANCE Ultra NH₂-(ULight)-CSETDDYAEIID-COOH (SEQ ID NO: 2) (C = cysteine S = serine, E = glutamic acid, T = threonine, D = aspartic acid, Y = tyrosine, A = alanine, I = isoleucine) substrate (purchased from Perkin Elmer Life Sciences). To measure inhibitors of FAK, compounds were first prepared as a 100X stock in 100% DMSO. A small portion of each compound solution (50 nL) was added to a black 384-well low-volume microtiter plate (Greiner 784076). A 1.2nM Flag-His-TEV-FAK1 solution was prepared in 1X reaction buffer containing 40mM Tris/Tris-HCL, 10mM MgCl₂, 1mM CHAPS, at a pH of 7.5, with 1mM DTT added. 2.5ul of the 1.2 nM Flag-FAK solution was added to the plates and pre-incubated with the compounds for 30 min at room temperature. Then, 2.5 μL of substrate solution (0.1 μM of P2 FAK-tide specific substrate (Lance Ultra NH₂-(ULight)-CSETDDYAEIID-COOH (SEQ ID NO: 2) from Perkin Elmer), 10μM ATP and the 1x reaction buffer described above), was added to the plate to initiate the reaction. After incubating for 120 minutes at room temperature, the reaction is quenched by adding 5 uL of 20mM EDTA and 5nMEu-Anti-pTyr antibody in 1X LANCE detection buffer. After a 30 minute incubation at room temperature, the plate is read on a Perkin Elmer Viewlux with a 320-340nm excitation filter and measuring emission at 615nm and 665nm. The ratio of 665nm/615nm is used for data normalization.

The following Table A provides specific data for compounds of the below Examples as run in one or both of the foregoing assays. These data were generated in at least one

run in the noted assay; repeats assay runs may have given or may give readouts that vary to some degree from these data.

Table A

Example No.	Assay 1 FAK TRF PXC ₅₀	Assay 2 FAK H 31284A TRF PXC ₅₀
1	8.7	7.8
2	8.8	8
3	9.2	8.3
4	9	8.2
5	9	8.1
6	8.9	8.3
7	9.1	8
8	9.2	8.3
9	9	8.2
10	9.1	8
11	8.7	8.2
12	8.6	8.3
13	9.3	8.7
14	8.6	7.7
15	8.6	7.7
16	8.9	7.7
17	8.9	7.4
18	8	
19	8.3	7.2
20	8	7.4
21	8.5	7.2
22	7.5	6.6
23	7.1	6.7
24	8.2	7.2
25	8.6	7.5
26	9.4	8.4
27	8.7	8.1
28	9.4	8.6
29	9.3	8.7
30	9.4	8.8
31	8.4	
32	9.4	9
33	9.4	
34	9.3	
36	9.4	8.8
37	8.4	7.7
38	6.6	6
39	9.4	8.3
40	8.9	8.6
41	9.4	8.7
42	7.9	7.3
43	8.3	7.6

Example No.	Assay 1 FAK TRF PXC ₅₀	Assay 2 FAK H 31284A TRF PXC ₅₀
44	8.2	7.2
45	8	7.2
46		7.9
47		8.6
49		7.2
50		7.9
51		7.7
52		8.2
53		7.4
54		7.5
55		8
56		7.8
58		7.3
59	9.2	8.3
60		7.9
61		7.6
62		
63		7.3
64		7.1
65		7.8
66	8.7	7.5
67	7.2	8.3
69		8.6
70		8.2
71		8.2
72		8.6
73		8.9

Chemistry Examples

The following chemistry examples are for illustrative purposes only and are not intended to limit the scope of the present invention. The compounds were named using ACD Name software (Advanced Chemistry Development, www.acdlabs.com). All compounds have pIC₅₀ of greater than 6.5 for the above-described biochemical assay.

A PE Sciex API 150 single quadrupole mass spectrometer (PE Sciex, Thornhill, Ontario, Canada) was operated using electrospray ionization in the positive ion detection mode. The nebulizing gas was generated from a zero air generator (Balston Inc., Haverhill, MA; www.parker.com) and delivered at 65 psi and the curtain gas was high purity nitrogen delivered from a Dewar liquid nitrogen vessel at 50 psi. The voltage applied to the electrospray needle was 4.8 kV. The orifice was set at 25 V and mass spectrometer was scanned at a rate of 0.5 scan/sec using a step mass of 0.2 amu and collecting profile data.

Method A, LCMS. Samples are introduced into the mass spectrometer using a CTC PAL autosampler (LEAP Technologies, Carrboro, NC) equipped with a hamilton 10 uL syringe which

performed the injection into a Valco 10-port injection valve. The HPLC pump was a Shimadzu LC-10ADvp (Shimadzu Scientific Instruments, Columbia, MD) operated at 0.3 mL/min and a linear gradient 4.5% A to 90% B in 3.2 min, with a 0.4 min. hold. The mobile phase was composed of 100% (H₂O 0.02% TFA) in vessel A and 100% (CH₃CN 0.018% TFA) in vessel B.

- 5 The stationary phase is Aquasil (C18) and the column dimensions are 1 mm x 40 mm. Detection was by UV at 214 nm, evaporative light-scattering (ELSD) and MS.

Method B, LCMS. Alternatively, an Agilent 1100 analytical HPLC system with an LC/MS was used and operated at 1 mL/min and a linear gradient 5% A to 100% B in 2.2 min with a 0.4 min hold. The mobile phase was composed of 100% (H₂O 0.02% TFA) in vessel A and
10 100% (CH₃CN 0.018% TFA) in vessel B. The stationary phase was Zorbax (C8) with a 3.5 μ m particle size and the column dimensions were 2.1 mm x 50 mm. Detection was by UV at 214 nm, evaporative light-scattering (ELSD) and MS.

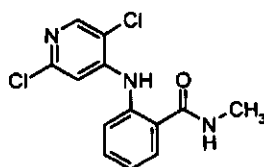
Method B, LCMS. Alternatively, an MDSSCIEX API 2000 equipped with a capillary column of (50 x 4.6 mm, 5 μ m) was used. HPLC was done on Agilent-1200 series UPLC system
15 equipped with column Zorbax SB-C18 (50 x 4.6 mm, 1.8 μ m) eluting with CH₃CN: ammonium acetate buffer. The reactions were performed in the microwave (CEM, Discover).

¹H-NMR (hereinafter "NMR") spectra were recorded at 400 MHz using a Bruker AVANCE 400 MHz instrument, with ACD Spect manager ver 10 using for reprocessing. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd = doublet of
20 doublets, dt=doublet of triplets etc. and br indicates a broad signal.

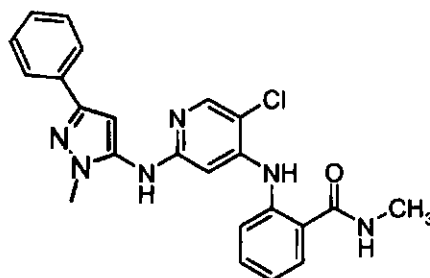
Analytical HPLC: Products were analyzed by Agilent 1100 Analytical Chromatography system, with 4.5 x 75 mm Zorbax XDB-C18 column (3.5 μ m) at 2 mL/min with a 4 min gradient from 5% CH₃CN (0.1% formic acid) to 95% CH₃CN (0.1% formic acid) in H₂O (0.1% formic acid) and a 1 min hold.

25 Preparative HPLC: Products were purified using a Gilson preparative chromatography system with a 75 x 30 mm I. D. YMC CombiPrep ODS-A column (5 μ m) (www.waters.com) at 50 mL/min with a 10 min gradient from 5% CH₃CN (0.1% formic acid) to 95% CH₃CN (0.1% formic acid) in H₂O (0.1% formic acid) and a 2 min hold; alternatively, products were purified using an Agilent 1100 Preparative Chromatography system, with 100 x 30 mm Gemini C18 column (5 μ m)
30 at 60 mL/min with a 10 min gradient from 5% CH₃CN (0.1% formic acid) to 95% CH₃CN (0.1% formic acid) in H₂O (0.1% formic acid) and a 2 min hold.

Preparative normal phase chromatography was carried out using an Analogix IntelliFlash 280 System with SuperFlash Septra Si 50 columns. Alternatively, reverse-phase HPLC was performed on Agilent using Zorbax SB - C18 column (21.2 x 250 mm, 7 μ m) eluting with CH₃CN:
35 ammonium acetate buffer (10 μ M) at pH 6.8.

ExamplesExample 11a) 2-[(2,5-Dichloro-4-pyridinyl)amino]-N-methylbenzamide

- 5 A 150-mL sealed tube was charged with 2,5-dichloro-4-iodopyridine (3.5 g, 12.78 mmol), 2-amino-N-methylbenzamide (1.919 g, 12.78 mmol) and tripotassium phosphate (8.14 g, 38.3 mmol) in 1,4-dioxane (100 mL). The reaction mixture was degassed with nitrogen for 10 min. Bis(2-diphenylphosphinophenyl)ether (DPEPhos, 0.688 g, 1.278 mmol) and Pd(OAc)₂ (0.115 g, 0.511 mmol) were added and the reaction mixture was heated in a 120° C oil bath over night. The
- 10 reaction mixture was filtered through celite, which was washed with dioxane. The solvent was evaporated to dryness and the solid was washed with EtOH (10 mL x 3) to give 2.14 g (56%) of product as an off white solid.

1b) 2-[5-Chloro-2-(2-methyl-5-phenyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methyl-benzamide

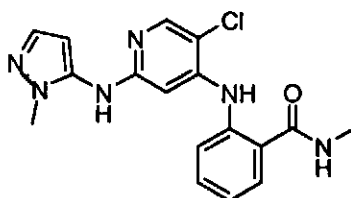
- 15 A 50-mL sealed tube was charged with Pd(OAc)₂ (18 mg, 0.08 mmol) and 2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (BINAP, 50 mg, 0.08 mmol) in 1,4-dioxane (10 mL). The mixture was degassed using bubbling nitrogen for 40 min and heated at 50° C for 1h. Then the mixture was cooled to room temperature whereupon 2-[(2,5-dichloro-4-pyridinyl)amino]-N-
- 20 methyl-benzamide (300 mg, 1.01 mmol), 2-methyl-5-phenyl-2H-pyrazol-3-ylamine (704 mg, 4.06 mmol) and cesium carbonate (960 mg, 2.96 mmol) were added under an inert atmosphere. The tube was sealed and heated at 120° C overnight. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, eluted with dichloromethane-methanol (DCM-MeOH) 99:1 followed by purification by preparatory TLC
- 25 to afford the desired compound as a off white solid (25 mg, 5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.76 (d, 3H, *J* = 4.52 Hz), 3.68 (s, 3H), 6.69 (s, 1 H), 6.85 (s, 1H), 7.07-7.14 (m, 1 H), 7.25-7.31 (m, 1H), 7.36-7.42 (m, 2H), 7.46-7.53 (m, 1 H), 7.63 (d, 1H, *J* = 8.08 Hz), 7.69 (d, 1H, *J* = 7.4

Hz), 7.75 (d, 2 H, J = 7.16 Hz), 8.04 (s, 1H), 8.69 (brs, 1H), 8.81 (s, 1H), 10.13 (s, 1H). LC-MS calculated for $C_{23}H_{21}ClN_6O$ (M + H) 433.15, found 433.3. HPLC purity 96 % at λ = 200 nm and 99 % at λ = 260 nm.

5

Example 22-({5-Chloro-2-[(1-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide

10



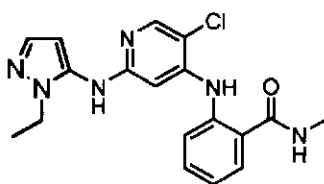
15

A mixture of 2-[(2,5-dichloro-4-pyridinyl)amino]-N-methylbenzamide (100 mg, 0.338 mmol), 5-amino-1-methyl-1H-pyrazole (65.6 mg, 0.675 mmol), Cs_2CO_3 (220 mg, 0.675 mmol), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 61.8 mg, 0.068 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 48.8 mg, 0.084 mmol) was heated at 150° C in a microwave oven for 30 min. The reaction mixture was filtered, and the filtrate was concentrated, and the resulting crude product was purified by reverse phase HPLC and the product was treated with 2 N HCl to give 34 mg of product as an HCl salt (24%). LCMS (ES) m/z = 357.1(M+H); ^1H NMR (400 MHz, methanol- d_4) δ ppm 8.01 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.61 (m, 2H), 7.55 (d, J = 2Hz, 1H), 7.42-7.39 (m, 1H), 6.52 (s, 1H), 6.33 (d, J=2Hz, 1H), 3.76 (s, 3H), 2.91 (s, 3H).

20

Example 32-({5-Chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide

25

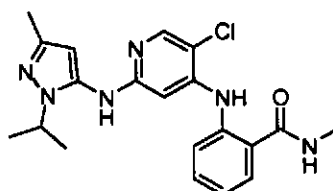


The title compound was prepared substantially as described in Example 2 except using 5-amino-1-ethyl-1H-pyrazole instead of 5-amino-1-methyl-1H-pyrazole. LCMS (ES) m/z = 371.1(M+H); ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 8.06 (m, 1H), 7.77-7.61 (m, 4H), 7.44-7.40 (m, 1H), 6.61 (m, 1H), 6.40 (s, 1H), 4.17-4.10 (m, 2H), 2.91 (s, 3H), 1.40 (tr, J=7.2Hz, 3H).

30

Example 4

2-[(5-Chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-methylbenzamide

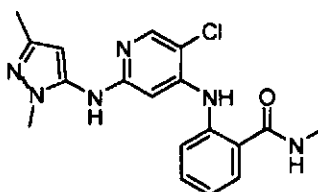


5 The title compound was prepared following the procedure in Example 2 except using 5-amino-1-isopropyl-1H-pyrazole instead of 5-amino-1-methyl-1H-pyrazole. LCMS (ES) m/z = 399.2(M+H); ^1H NMR (400 MHz, methanol- d_4) δ ppm 8.06 (s, 1H), 7.78-7.76 (m, 1H), 7.65-7.63 (m, 2H), 7.45-7.38 (m, 1H), 6.64 (s, 1H), 6.29 (s, 1H), 4.70-4.55 (m, 1H), 2.91 (s, 3H), 2.34 (s, 1H), 1.47(d, J=6.8Hz, 6H).

10

Example 5

2-[(5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-methylbenzamide

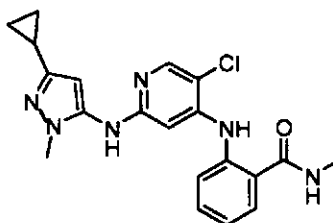


The title compound was prepared following the procedure in Example 2 except using 5-amino-1-methyl-3-methyl-1H-pyrazole instead of 5-amino-1-methyl-1H-pyrazole. LCMS (ES) m/z = 371.1 (M+H); ^1H NMR (400 MHz, methanol- d_4) δ ppm 8.12 (s, 1H), 7.78-7.76 (d, J = 7.6Hz, 1H), 7.66-7.64 (m, 2H), 7.45-7.41 (m, 1H), 6.67 (s, 1H), 6.38 (s, 1H), 3.80 (s, 3H), 2.91 (s, 3H), 2.35 (s, 3H).

20

Example 6

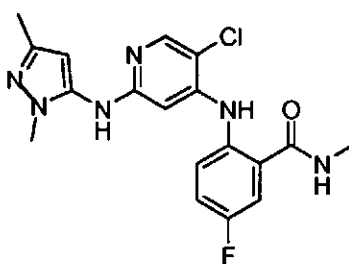
2-[(5-Chloro-2-[(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-methylbenzamide



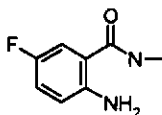
The title compound was prepared following the procedure in Example 2 except using 5-amino-3-cyclopropyl-1-methyl-1H-pyrazole instead of 5-amino-1-methyl-1H-pyrazole. LCMS (ES) $m/z = 397.1 (M+H)$; ^1H NMR (400 MHz, methanol- d_4) δ ppm 8.06 (s, 1H), 7.78-7.76 (m, 1H), 7.64-7.62 (m, 2H), 7.44-7.40 (m, 1H), 6.57 (s, 1H), 6.15 (s, 1H), 3.71 (s, 3H), 2.91 (s, 3H), 1.97-1.90 (m, 1H), 1.04-1.00 (m, 2H), 0.79-0.76 (m, 2H).

Example 7

2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-fluoro-N-methylbenzamide



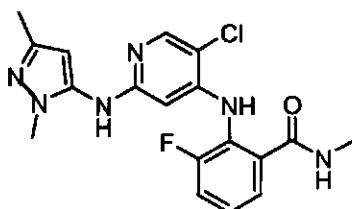
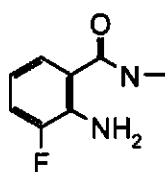
7a) 2-Amino-5-fluoro-N-methylbenzamide



6-Fluoro-2H-3,1-benzoxazine-2,4(1H)-dione (200 mg, 1.104 mmol) was dissolved in dry tetrahydrofuran (THF) (10 mL), at which time methyl amine (3.31 mL, 6.63 mmol) was added. The reaction was stirred at room temperature for 1 h, then concentrated under vacuum. The crude product was purified on silica (Biotage, 40% EtOAc/hexene) to afford the title compound (120 mg, 65%) as a white solid. LC-MS (ES) $m/z = 169.1 (M+H)^+$

7b) 2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-fluoro-N-methylbenzamide

The title compound was prepared as a white solid by first reacting 2-amino-5-fluoro-N-methylbenzamide with 2,5-dichloro-4-iodopyridine to form 2-[(2,5-dichloro-4-pyridinyl)amino]-5-fluoro-N-methylbenzamide substantially according to the procedure of Intermediate 1, then reacting this intermediate with 1,3-dimethyl-1H-pyrazol-5-amine substantially according to the procedure of Example 2. : LC-MS (ES) $m/z = 389.1 (M+H)^+$, ^1H NMR (CD_3OD , 400 MHz) δ 8.01 (s, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.38 (m, 1H), 6.39 (s, 1H), 6.18 (s, 1H), 3.69 (s, 3H), 2.89 (s, 3H), 2.24 (s, 3H)

Example 82-({5-Chloro-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide5 8a) 2-Amino-3-fluoro-*N*-methylbenzamide

2-Amino-3-fluorobenzonitrile (3.8 g, 27.9 mmol) was dissolved in ethanol, water (15 mL) and THF (0.3 mL), potassium hydroxide (7.83 g, 140 mmol) was added. The mixture was heated at 85° C for 12 h, cooled and filtered. The filtrate was concentrated and the residue was dissolved in dichloromethane (DCM, 50 mL). Then diisopropylethylamine (19.50 mL, 112 mmol) was added, followed by methyl amine (20.94 ml, 41.9 mmol) and bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP, 21.79 g, 41.9 mmol). The reaction was stirred at room temperature for 2 h, washed with brine and dried over MgSO₄. The solvent was removed and the residue was purified by chromatography on silica gel (20% EtOAc/Hex) to give 1.5 g (35% yield) of intermediate a.

8b). 2-({5-Chloro-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

The title compound was prepared as a white solid according to the procedure of Example 7, except using 2-amino-3-fluoro-*N*-methylbenzamide in place of 2-amino-5-fluoro-*N*-methylbenzamide: LC-MS (ES) $m/z = 389.1$ ($M+H$)⁺, ¹H NMR (CD₃OD, 400 MHz) δ 8.01 (s, 1H), 7.50 (m, 3H), 6.14 (s, 1H), 5.87 (m, 1H), 3.65 (s, 3H), 2.89 (s, 3H), 2.22 (s, 3H)

The 2-{{5-chloro-2-(amino pyrazole)-4-pyridinyl}amino}-benzamide compounds illustrated in Table 1 were prepared from various 2-[(2,5-dichloro-4-pyridinyl)amino]-methylbenzamides and amino-pyrazoles substantially according to the procedure of Example 7. In the following tables, the dashed lines indicate the points of attachment. Thus, for Example 9, the compound corresponds to the following structure:

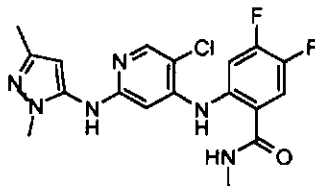
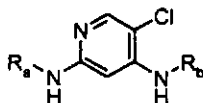
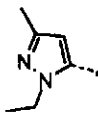
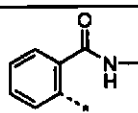
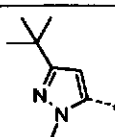
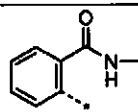
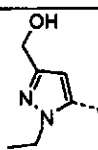
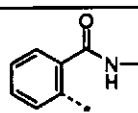
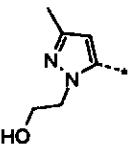
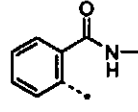


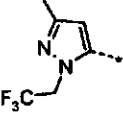
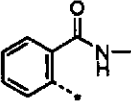
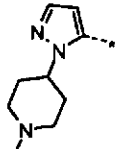
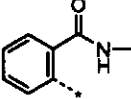
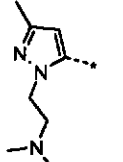
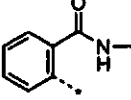
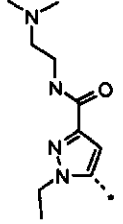
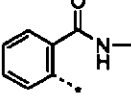
Table 1

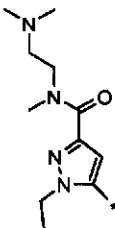
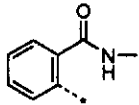
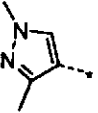
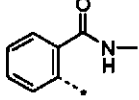
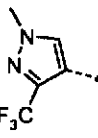
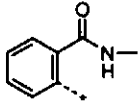


Ex.	Name	R _a	R _b	Data
9	2-({5-Chloro-2-[(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)amino]-4-pyridinyl} amino)-4,5-difluoro- <i>N</i> -methylbenzamide			LC-MS (ES) <i>m/z</i> = 407.1 (<i>M</i> + <i>H</i>) ⁺ , ¹ H NMR (CD ₃ OD, 400 MHz) δ 8.04 (s, 1H), 7.71 (m, 1H), 7.61 (m, 1H), 6.63 (s, 1H), 6.28 (s, 1H), 3.72 (s, 3H), 2.89 (s, 3H), 2.72 (s, 3H)
10	2-({5-Chloro-2-[(1-ethyl-1 <i>H</i> -pyrazol-5-yl)amino]-4-pyridinyl} amino)-4,5-difluoro- <i>N</i> -methylbenzamide			LC-MS (ES) <i>m/z</i> = 460.1 (<i>M</i> + <i>H</i>) ⁺ , ¹ H NMR (CD ₃ OD, 400 MHz) δ 8.00 (s, 1H), 7.70 (m, 1H), 7.59 (m, 2H), 6.56 (s, 1H), 6.33 (s, 1H), 4.11 (m, 2H), 2.90 (m, 3H), 1.38 (m, 3H)
11	5-Chloro-2-({5-chloro-2-[(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)amino]-4-pyridinyl} amino)- <i>N</i> -methylbenzamide			LC-MS (ES) <i>m/z</i> = 407.0 (<i>M</i> + <i>H</i>) ⁺ , ¹ H NMR (CD ₃ OD, 400 MHz) δ 8.03 (s, 1H), 7.78 (m, 1H), 7.61 (m, 2H), 6.56 (s, 1H), 6.23 (s, 1H), 3.70 (s, 3H), 2.90 (s, 3H), 2.26 (s, 3H)
12	5-Chloro-2-({5-chloro-2-[(1-ethyl-1 <i>H</i> -pyrazol-5-yl)amino]-4-pyridinyl} amino)- <i>N</i> -methylbenzamide			LC-MS (ES) <i>m/z</i> = 407.0 (<i>M</i> + <i>H</i>) ⁺ , ¹ H NMR (CD ₃ OD, 400 MHz) δ 8.00 (s, 1H), 7.78 (m, 1H), 7.59 (m, 3H), 6.50 (s, 1H), 6.32 (m, 1H), 4.10 (m, 2H), 2.89 (s, 3H), 1.37 (s, 3H)

Ex.	Name	R _a	R _b	Data
13	2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide			LCMS (ES) m/z = 384.8(M+H); 1H NMR (400 MHz, METHANOL- <i>d</i> ₄) δppm 8.01 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.61 (m, 2H), 7.41-7.37 (m, 1H), 6.59 (s, 1H), 6.20 (s, 1H), 4.07-4.01 (m, 2H), 2.91 (s, 3H), 2.27 (s, 3H), 1.35(tr, J=7.2 Hz, 3H).
14	2-[(5-Chloro-2-{[3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-methylbenzamide			LCMS (ES) m/z = 412.8(M+H); 1H NMR (400 MHz, METHANOL- <i>d</i> ₄) δppm 8.05 (s, 1H), 7.75-7.72 (m, 1H), 7.60-7.58 (m, 2H), 7.40-7.35 (m, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 3.70 (s, 3H), 2.91 (s, 3H), 1.30 (s, 9H).
15	2-[(5-Chloro-2-{[1-ethyl-3-(hydroxymethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-methylbenzamide			LCMS (ES) m/z = 401.1(M+H); 1H NMR (400 MHz, METHANOL- <i>d</i> ₄) δppm 7.99 (s, 1H), 7.75-7.73 (m, 1H), 7.61-7.59 (m, 2H), 7.39-7.35 (m, 1H), 6.58 (s, 1H), 6.31 (s, 1H), 4.56 (s, 2H), 4.08-4.03 (m, 2H), 2.91 (s, 3H), 1.36(tr, J=7.2Hz, 6H).
16	2-[(5-Chloro-2-{[1-(2-hydroxyethyl)-3-methyl-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-methylbenzamide			LCMS (ES) m/z = 401.1(M+H); 1H NMR (400 MHz, METHANOL- <i>d</i> ₄) δppm 8.07 (s, 1H), 7.78-7.76 (m, 1H), 7.65-7.63 (m, 2H), 7.43-7.39 (m, 1H), 6.69 (s, 1H), 6.31 (s, 1H), 4.18 (tr, J=5.2Hz, 2H), 3.85 (tr, J=5.2Hz, 2H), 2.91 (s, 3H), 2.32 (s, 3H).

Ex.	Name	R _a	R _b	Data
17	Ethyl 5-{{[5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl]amino}-1-ethyl-1H-pyrazole-3-carboxylate			LCMS (ES) m/z = 443.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.02 (s, 1H), 7.75-7.74 (m, 1H), 7.62-7.60 (m, 2H), 7.40-7.36 (m, 1H), 6.82 (s, 1H), 6.59 (s, 1H), 4.41-4.36 (m, 2H), 4.19-4.14 (m, 2H), 2.91 (s, 3H), 1.43-1.37(m, 6H).
18	5-{{[5-Chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl]amino}-1-ethyl-1H-pyrazole-3-carboxylic acid			LCMS (ES) m/z = 415.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.02 (s, 1H), 7.78-7.76 (m, 1H), 7.65-7.63 (m, 2H), 7.44-7.40 (m, 1H), 6.83 (s, 1H), 6.59 (s, 1H), 4.20-4.14 (m, 2H), 2.91 (s, 3H), 1.42(tr, J=6.8Hz, 3H).
19	5-{{[5-Chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl]amino}-1-ethyl-N-(methyloxy)-1H-pyrazole-3-carboxamide			LCMS (ES) m/z = 444.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.01 (s, 1H), 7.76-7.74 (m, 1H), 7.63-7.62 (m, 2H), 7.41-7.37 (m, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 4.16-4.13 (m, 2H), 3.81 (s, 3H), 2.91 (s, 3H), 1.42(tr, J=6.8Hz, 3H).
20	5-{{[5-Chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl]amino}-1-ethyl-N-methyl-1H-pyrazole-3-carboxamide			LCMS (ES) m/z = 428.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.01 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.61 (m, 2H), 7.41-7.38 (m, 1H), 6.71 (s, 1H), 6.55 (s, 1H), 4.16-4.10 (q, J=7.2Hz, 2H), 2.92 (s, 3H), 2.91 (s, 3H), 1.42(tr, J=7.2Hz, 3H).

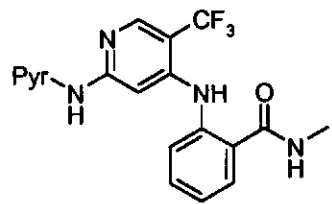
Ex.	Name	R _a	R _b	Data
21	2-[(5-Chloro-2-[[3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl]amino]-N-methylbenzamide			LCMS (ES) m/z = 439.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.00 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.58 (m, 2H), 7.40-7.36 (m, 1H), 6.61 (s, 1H), 6.25 (s, 1H), 4.82-4.76 (q, J=8.4Hz, 2H), 2.91 (s, 3H), 2.27(s, 3H).
22	2-[(5-Chloro-2-[[1-(1-methyl-4-piperidinyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl]amino]-N-methylbenzamide			LCMS (ES) m/z = 440.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.04 (s, 1H), 7.75-7.73 (m, 1H), 7.61-7.57 (m, 3H), 7.42-7.38 (m, 1H), 6.45 (s, 1H), 6.33 (s, 1H), 4.60-4.50 (m, 1H), 3.67-3.63 (m, 2H), 3.25-3.15 (m, 2H), 2.91 (s, 3H), 2.90 (s, 3H), 2.40-2.12 (m, 4H).
23	2-[[5-Chloro-2-([1-[2-(dimethylamino)ethyl]-3-methyl-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino]-N-methylbenzamide			LCMS (ES) m/z = 428.1(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.06 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.61 (m, 2H), 7.43-7.38 (m, 1H), 6.59 (s, 1H), 6.18 (s, 1H), 4.41-4.38 (t, J=5.6Hz, 2H), 3.63-3.60 (t, J=5.6Hz, 2H), 2.98 (s, 6H), 2.91 (s, 3H), 2.25 (s, 3H).
24	5-[[5-Chloro-4-([2-[(methylamino)carbonyl]phenyl]amino)-2-pyridinyl]amino]-N-[2-(dimethylamino)ethyl]-1-ethyl-1H-pyrazole-3-			LCMS (ES) m/z = 485.2(M+H); 1H NMR (400 MHz, METHANOL-d ₄) δppm 8.03 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.60 (m, 2H), 7.40-7.35 (m, 1H), 6.76 (s, 1H), 6.56 (s, 1H), 4.16-4.14 (q,

	carboxamide			J=7.2Hz, 2H), 3.77 (tr, J=6.0Hz, 2H), 3.38 (tr, J=6.0Hz, 2H), 2.99(s, 6H), 2.91 (s, 3H), 1.42(tr, J=7.2Hz, 3H).
25	5-{{5-Chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino}-N-[2-(dimethylamino)ethyl]-1-ethyl-N-methyl-1H-pyrazole-3-carboxamide			LCMS (ES) m/z = 499.2(M+H); ¹ H NMR (400 MHz, METHANOL-d ₄) δppm 8.04 (s, 1H), 7.76-7.74 (m, 1H), 7.62-7.60 (m, 2H), 7.40-7.35 (m, 1H), 6.70 (s, 1H), 6.52 (s, 1H), 4.16-4.10 (m, 2H), 3.95-3.90 (m, 1H), 3.58-3.40 (m, 5H), 3.20-3.15 (m, 1H), 3.03 (s, 6H), 2.91 (s, 3H), 1.42(tr, J=7.2Hz, 3H).
26	2-{{5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino}-N-methylbenzamide			LC-MS (ES) m/z = 371.1 (M+H) ⁺ ; ¹ H NMR (CD ₃ OD, 400 MHz) δ 7.88 (s, 1H), 7.84 (s, 1H), 7.75 (m, 1H), 7.64 (m, 2H), 7.40 (m, 1H), 6.58 (s, 1H), 3.92 (s, 3H), 2.92 (s, 3H), 2.18 (s, 3H)
27	2-{{5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino}-N-methylbenzamide			LC-MS (ES) m/z = 425.0 (M+H) ⁺ ; ¹ H NMR (CD ₃ OD, 400 MHz) δ 7.98 (s, 1H), 7.90 (s, 1H), 7.76 (m, 1H), 7.63 (m, 2H), 7.40 (m, 1H), 6.58 (s, 1H), 4.00 (s, 3H), 2.91 (s, 3H)

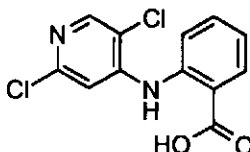
The 2-{{5-trifluoromethyl-2-(aminopyrazole)-4-pyridinyl}amino}-benzamide compounds illustrated in Table 2 were prepared from 2-[(2-chloro-5-trifluoromethyl-4-pyridinyl)amino]-methylbenzamide and the corresponding amino-pyrazole substantially according to the procedure of Example 2.

5

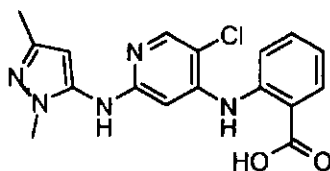
Table 2



Ex	Name	Pyr	Data
28	2-{{2-[(1,3-Dimethyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino}- <i>N</i> -methylbenzamide		LC-MS (ES) <i>m/z</i> = 405.1 (M+H) ⁺
29	2-{{2-[(1-Ethyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino}- <i>N</i> -methylbenzamide		LC-MS (ES) <i>m/z</i> = 405.1 (M+H) ⁺
30	<i>N</i> -Methyl-2-{{2-{{3-methyl-1-(1-methylethyl)-1 <i>H</i> -pyrazol-5-yl}amino}-5-(trifluoromethyl)-4-pyridinyl}amino}benzamide		LC-MS (ES) <i>m/z</i> = 433.2 (M+H) ⁺
31	2-{{2-{{1-[2-(Dimethylamino)ethyl]-3-methyl-1 <i>H</i> -pyrazol-5-yl}amino)-5-(trifluoromethyl)-4-pyridinyl}amino}- <i>N</i> -methylbenzamide		LC-MS (ES) <i>m/z</i> = 462.2 (M+H) ⁺
32	2-{{2-[(1-Ethyl-3-methyl-1 <i>H</i> -pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino}- <i>N</i> -methylbenzamide		LCMS (ES) <i>m/z</i> = 419.2 (M+H)
33	<i>N</i> -Methyl-2-{{2-{{3-methyl-1-phenyl-1 <i>H</i> -pyrazol-5-yl}amino)-5-(trifluoromethyl)-4-pyridinyl}amino}benzamide		LCMS (ES) <i>m/z</i> = 467.1(M+H)
34	2-{{2-{{1-(2-hydroxyethyl)-3-methyl-1 <i>H</i> -pyrazol-5-yl}amino)-5-(trifluoromethyl)-4-pyridinyl}amino}- <i>N</i> -methylbenzamide		LCMS (ES) <i>m/z</i> = 435.1(M+H)

Intermediate 12-[(2,5-Dichloro-4-pyridinyl)amino]benzoic acid

A mixture of 2,5-dichloro-4-iodopyridine (10 g, 36.5mmol), 2-aminobenzoic acid (4.85g, 35.4mmol), DPEPhos [bis(2-diphenylphosphinophenyl)ether] (1.6g, 2.97mmol), palladium(II) acetate (160 mg, 0.713mmol) and K_3PO_4 (20g, 94mmol) was degassed and heated at 120 °C (oil bath temp) for 20 h. After 20 h, LCMS showed there was 33% (relative to the desired product) starting material left. Added another 160 mg of $Pd(OAc)_2$ to the mixture, and heated to 120 °C for another 24 h. LCMS showed conversion complete. The mixture was cooled to room temperature, followed by filtration, and washing with EtOAc. The solids were acidified to pH = 7-8, followed by filtration. However, the mixture was a paste, and collected solids could not be dried completely. The solids (11 g) was acidified with 6N HCl to pH=1. The resulting paste was filtered, and washed with water and TBME. The solid was dried under vacuum over P_2O_5 for 2 days to give the title compound (7.32 g, 60.2% yield). MS: $M(C_{12}H_8Cl_2N_2O_2) = 283.11$, $(M+H)^+ = 283.8$; ^1H NMR (400 MHz, DMSO) δ ppm 13.6 (s, 1 H) 10.2 (s, 1 H) 8.3 (s, 1 H) 8.0 (d, 1 H) 7.6 (q, 2 H) 7.3 (s, 1 H) 7.2 (m, 1 H).

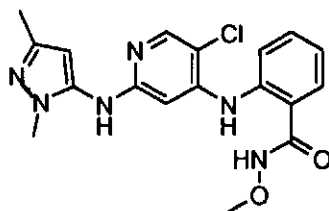
Example 352-[(5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]benzoic acid

A pressure tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]benzoic acid (1.0 g, 3.53 mmol), 1,3-dimethyl-1H-pyrazol-5-amine (0.589 g, 5.30 mmol), ($\pm$)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (0.330 g, 0.530 mmol), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 0.162 g, 0.177 mmol) and sodium tert-butoxide (0.849 g, 8.83 mmol) in 1,4-dioxane (30 mL). The tube was degassed with N_2 and sealed and the reaction mixture was heated in an oil bath at 120° C for 18 hours. The reaction mixture was evaporated to dryness under high vacuum. The residue was taken back in water solution and the pH was adjusted to ~ 4 to 5 using 6.0 N hydrochloride acid. The reaction was concentrated to dryness and the resulting solid was dissolved in MeOH and purified by reverse-phase HPLC to

give the title compound as a solid (285 mg, 21% yield). MS: $M(C_{17}H_{16}ClN_5O_2) = 357.79$, $(M+H)^+ = 358, 360$.

Example 36

5 2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methoxy)benzamide

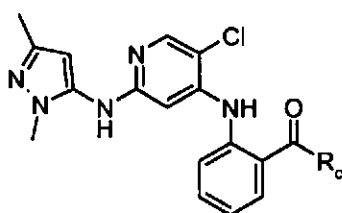


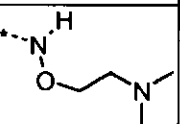
A vessel was charged with 3-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid (100 mg, 0.279 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53.6 mg, 0.279 mmol) and hydroxybenzotriazole (42.8 mg, 0.279 mmol) in N,N-dimethylformamide (DMF, 1.0 mL) and the contents were stirred at room temperature for 30 min. Methoxylamine hydrochloride (23.34 mg, 0.279 mmol) was added to this mixture and stirring continued for another 10 min. The reaction mixture was cooled to 0° C. Diisopropylethylamine (DIEA, 0.098 mL, 0.559 mmol) was added and the reaction mixture was stirred at room temperature overnight. The final crude material was purified using reverse-phase HPLC, (Gilson) eluted with CH₃CN/H₂O with 0.1% formic acid to yield 15 mg (18% yield) MS: $M(C_{18}H_{19}ClN_6O_2) = 386.84$, $(M+H)^+ = 387$; ¹H NMR (400 MHz, MeOD) δ ppm 8.16 (s, 1 H) 7.93 (s, 1 H) 7.50 - 7.66 (m, 2 H) 7.11 - 7.25 (m, 1 H) 6.62 (s, 1 H) 5.99 (s, 1 H) 3.80 (s, 3 H) 3.55 - 3.70 (s, 3 H) 2.11 - 2.26 (s, 3 H).

20 The 2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-alkyl-N-(alkyloxy)benzamide compounds illustrated in Table 3 were prepared from 3-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid and amino-alcohols substantially according to the procedure of Example 36.

25

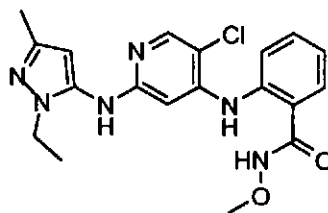
Table 3



Ex	Name	R _c	Data
37	2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl) amino]-4-pyridinyl} amino)-N-methyl-N-(methoxy)benzamide		LC-MS (ES) m/z = 387 (M+H) ⁺ ; ¹ H NMR (400 MHz, MeOD) δ ppm 8.16 (s, 1 H) 7.93 (s, 1 H) 7.50 - 7.66 (m, 2 H) 7.11 - 7.25 (m, 1 H) 6.62 (s, 1 H) 5.99 (s, 1 H) 3.80 (s, 3 H) 3.55 - 3.70 (s, 3 H) 2.11 - 2.26 (s, 3 H)
38	2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl} amino)-N-{[2-(dimethylamino)ethyl]oxy}benzamide		LC-MS (ES) m/z = 444, 446 (M+H) ⁺ ; ¹ H NMR (400 MHz, MeOD) δ ppm 8.50 (s, 1 H) 7.93 (s, 1 H) 7.64 - 7.71 (m, 1 H) 7.51 - 7.61 (m, 2 H) 7.21 (ddd, J = 8.0, 6.2, 2.3 Hz, 1 H) 6.58 (s, 1 H) 5.98 (s, 1 H) 4.22 - 4.31 (m, 2 H) 3.61 (s, 3 H) 3.33 - 3.40 (m, 2H) 2.96 (s, 6 H) 2.19 (s, 3 H)

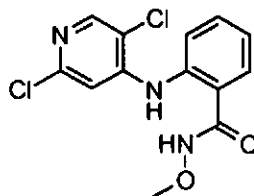
Example 39

2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl} amino)-N-(methoxy)benzamide



5

39a) 2-[(2,5-Dichloro-4-pyridinyl)amino]-N-(methoxy)benzamide



A vessel was charged with 3-[(2,5-dichloro-4-pyridinyl)amino]benzoic acid (1.0g, 3.53 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (677 mg, 3.53 mmol) and hydroxybenzotriazole (HOBt) (541 mg, 3.53 mmol) in N,N-dimethylformamide (DMF, 7.0 mL) and was stirred at room temperature for 30 min. To this solution methoxylamine hydrochloride (0.3 g, 3.53 mmol) was added and reaction mixture was stirred for another 10 min. The reaction

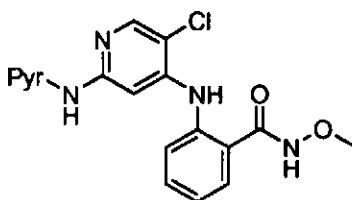
mixture was cooled to 0° C by using an ice bath. To this reaction mixture diisopropylethylamine (1.2 mL, 7.06 mmol) was added and the mixture was stirred at room temperature overnight. After concentrating under vacuum, the residue was worked up by using a saturated aqueous solution of NaHCO₃ and CH₂Cl₂. The organic phase was washed with brine then dried over MgSO₄ and filtered. The CH₂Cl₂ was removed by rotary evaporation. The crude material was loaded on silica gel column and eluted by MeOH in CH₂Cl₂ with NH₄OH 0.1%, which gave the desired product 2-[(2,5-dichloro-4-pyridinyl) amino]-N-(methyloxy)benzamide (850 mg, 2.72 mmol, 77 % yield) MS: M(C₁₃H₁₁Cl₂N₃O₂) = 312.15, (M+H)⁺ = 312, 314; 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.57 (br. s., 1 H) 8.72 (s, 1 H) 8.22 (s, 1 H) 7.51 - 7.67 (m, 3H) 7.25 (s, 1 H) 7.07 - 7.21 (m, 1 H) 3.92 (s, 3 H).

39b) 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide

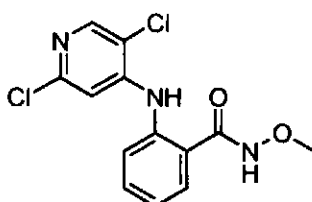
A 20-mL microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide (100 mg, 0.320 mmol), 1-ethyl-3-methyl-1H-pyrazol-5-amine (60.1 mg, 0.481 mmol), cesium carbonate (313 mg, 0.961 mmol), 1,4-dioxane (5.0 mL) and THF (1.0 mL). The reaction mixture was degassed by nitrogen for 10 min. (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (19.95 mg, 0.032 mmol) and Palladium(II) acetate (3.60 mg, 0.016 mmol) in minimum amount of 1,4-dioxane were then added. The tube was sealed and reaction mixture was heated in microwave oven 160° C for 40 min. The resulting suspension was cooled to room temperature and filtered through celite. The filtrate was evaporated to dryness and the crude reaction mixture was purified by reverse-phase HPLC to give the title compound as a solid (16 mg, 24%yield) MS: M(C₁₉H₂₁ClN₆O₂) = 400.86, (M+H)⁺ = 401; 1H NMR (400 MHz, MeOD) δ ppm 7.92 (s, 1 H) 7.44 - 7.66 (m, 3 H) 7.11 - 7.25 (m, 1 H) 6.61 (s, 1 H) 5.99 (s, 1 H) 3.98 (q, J=7.3 Hz, 2 H) 3.80 (s, 3 H) 2.21 (s, 3 H) 1.32 (t, J=7.2 Hz, 3 H).

The 2-({5-chloro-2-(pyrazol-5-yl)amino}-4-pyridinyl)amino)-N-(methyloxy)benzamide compounds illustrated in Table 4 were prepared from 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide and amino-pyrazoles substantially according to the procedure of Example 39.

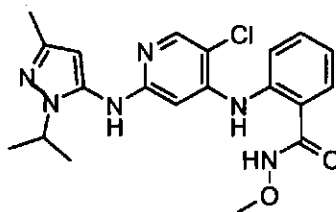
Table 4



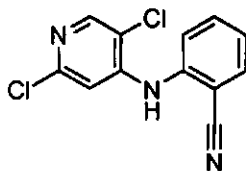
Ex	Name	Pyr	Data
40	2-({5-Chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide		LC-MS (ES) m/z = 387, 388 (M+H) ⁺ ; ¹ H NMR (400 MHz, MeOD) δ ppm 1H 7.90 - 7.96 (m, 1 H) 7.49 - 7.66 (m, 3 H) 7.45 (t, J=2.2 Hz, 1 H) 7.10 - 7.22 (m, 1 H) 6.61 (s, 1 H) 6.19 (d, J=1.8 Hz, 1 H) 4.06 (q, J=7.1 Hz, 2 H) 3.80 (s, 3 H) 1.35 (t, J=7.2 Hz, 3H)

Intermediate 22-[(2,5-Dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide

- 5 A solution of 3-[(2,5-dichloro-4-pyridinyl)amino]benzoic acid (500 mg, 1.766 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) (339 mg, 1.766 mmol) and 1-hydroxybenzotriazole (HOBT) (270 mg, 1.766 mmol) in N,N-dimethylformamide (3532 μl) was stirred at room temperature for 30 min. To this solution O-methylhydroxylamine (aminoxy)methane (148 mg, 1.766 mmol) was then added and stirred for another 10min. The
- 10 reaction mixture was cooled using an ice water bath. Then diisopropylethylamine (617 μl, 3.53 mmol) was added. After the addition was finished, the reaction mixture was stirred at room temperature overnight. The reaction mixture was followed by HPLC and LCMS. The final crude material was worked up by addition of saturated aqueous NaHCO₃ and CH₂Cl₂. Organic phase was washed with brine then dried over MgSO₄. The solution was filtered and solvent was removed by
- 15 evaporation. The oil like crude material was loaded on silica column and eluted with MeOH in CH₂Cl₂ with NH₄OH 0.1% to give the target compound 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide (320 mg, 1.025 mmol, 58.0 % yield) as a yellow solid; MS; M(C₁₃H₁₁Cl₂N₃O₂) = 312.15, (M+H)⁺ = 312, 313.9; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.66 (br. s., 1 H) 9.60 (br. s., 1 H) 8.20 (s, 1 H) 7.49 - 7.61 (m, 3 H) 7.24 (s, 1 H) 7.09 - 7.16
- 20 (m, 1 H) 3.90 (s, 3 H).

Example 41a2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-N-(methoxy)benzamide

- 5 A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methoxy)benzamide (70 mg, 0.224 mmol), {3-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (70 mg, 0.503 mmol) and cesium carbonate (230 mg, 0.706 mmol). The reaction mixture was degassed with nitrogen for 10 min. At same time, BINAP (50 mg, 0.080 mmol) and palladium(II) acetate (10 mg, 0.045 mmol) were added. The reaction mixture was heated in a microwave at 160
- 10 °C for 40 min. The crude material was purified on reverse-phase HPLC (Gilson) eluting with CH₃CN/H₂O with 0.1% formic acid which gave a title compound (15mg, 15%); MS: M(C₂₀H₂₃ClN₆O₂) = 414.89, (M+H)⁺ = 415, 416; ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.42 (br. s., 1 H) 8.71 (br. s., 1 H) 8.02 (s, 1 H) 7.54 (br. s., 1H) 7.06 (t, J=7.5 Hz, 1 H) 6.48 (s, 1 H) 6.32 (br. s., 1 H) 5.86 (s, 1 H) 4.47 (dt, J=13.4, 6.7 Hz, 1 H) 3.92 (s, 3 H) 2.26 (s, 3 H) 1.41 -
- 15 1.43 (d, J = 6.6 Hz, 2H).

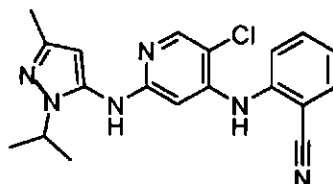
Intermediate 32-[(2,5-Dichloro-4-pyridinyl)amino]benzonitrile

- 20 The solution of 2,5-dichloro-4-iodopyridine (100 g, 365 mmol), 2-aminobenzonitrile (43.1 g, 365 mmol) and potassium triphosphate (233 g, 1095 mmol) in 1,4-dioxane (2.5 L) was degassed by N₂ stream. To this solution was added DPEPhos (15.73 g, 29.2 mmol) and palladium acetate (3.28 g, 14.60 mmol). The reaction mixture was stirred at reflux for 18 hour. The solution was filtered through 0.5 in. celite and 0.2 inch of silica. The solution was evaporated. Solid was
- 25 suspended in the diethyl ether and filtered. Diethyl ether was concentrated, and the resulting solid was filtered. 2-[(2,5-Dichloro-4-pyridinyl)amino]benzonitrile (80 g, 288 mmol, 79 % yield) was isolated as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 6.49 (s, 1 H) 7.50 (td, J=7.58,

1.01 Hz, 1 H) 7.56 (d, $J=7.58$ Hz, 1 H) 7.80 (td, $J=7.83$, 1.77 Hz, 1 H) 7.95 (dd, $J=7.83$, 1.52 Hz, 1 H) 8.26 (s, 1 H) 9.05 (brs, 1 H); HPLC $R_t=2.88$ min, MS (ESI): 263.9, 265.9 $[M+H]^+$.

Intermediate 4

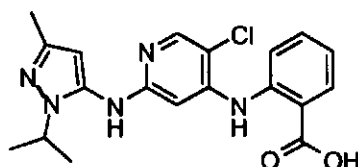
5 2-[(5-Chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino]benzonitrile



The solution of 2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (110 g, 396 mmol), 3-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (55.1 g, 396 mmol), and cesium carbonate (387 g, 1187 mmol) in 1,4-dioxane (2.5 L) was degassed by N_2 stream, and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (19.71 g, 31.7 mmol) followed by palladium acetate (3.55 g, 15.83 mmol) were added. The reaction mixture was heated to reflux for overnight under N_2 . The reaction mixture was filtered and the liquid was concentrated. Ethyl acetate (1500 mL), followed by 1 M HCl (1000 mL) were added. Layers were separated. Ethyl acetate was washed with 1 M HCl until no product was observed by HPLC (1000 mL total, 1 x). HCl phases were combined, and backwashed with ethyl acetate (3 x 1000 mL), until the product peak was relatively pure in the HCL layer. The HCl layer was then basified with NaOH (50 w/w followed by 1 M) to pH~4 resulting in a cloudy solution. Ethyl acetate (2000 mL) was added and layers were separated. The ethyl acetate was washed with brine and evaporated. After neutralization - after addition of ethyl acetate - the reaction mixture was filtered to get some product. Also isolation of product during evaporation can be done by filtration of white solid, which comes from the mother liquor. All solids and evaporated products were combined. 2-[(5-Chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino]benzonitrile (80 g, 207 mmol, 52.4 % yield) was isolated as a yellow solid. ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.24 (d, $J=6.57$ Hz, 6 H) 2.08 (s, 3 H) 4.34 (quin, $J=6.57$ Hz, 1 H) 5.87 (s, 1 H) 5.97 (s, 1 H) 7.41 (td, $J=7.58$, 1.01 Hz, 1 H) 7.47 (d, $J=8.08$ Hz, 1 H) 7.75 (td, $J=7.83$, 1.52 Hz, 1 H) 7.90 (dd, $J=7.83$, 1.52 Hz, 1 H) 7.94 (s, 1 H) 8.42 (d, $J=17.43$ Hz, 2 H); HPLC $R_t=2.36$ min, MS (ESI): $[M+H]^+=367.1$, 368.1.

Intermediate 5

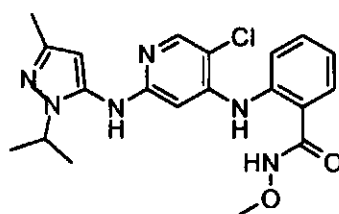
2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzoic acid



- 5 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzonitrile (80 g, 218 mmol) was dissolved in 1,4-dioxane (1.5 L) and 1 M NaOH (1500 mL, 1500 mmol) was added. The suspension was refluxed overnight. After cooling to RT, ethyl acetate (1 L) was added and layers were separated. The water layer was washed with 1 L of ethyl acetate. Both organic layers were combined and backwashed with 0.1 M NaOH (1 L)
- 10 until no product was observed in organic. The organics were then discarded. Combined aqueous were then washed with 1 L of ethyl acetate. The water layer was then acidified with acetic acid (very slowly to pH ~ 7). The solid was filtered and 2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzoic acid (67 g, 165 mmol, 76 % yield) was isolated as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.28 (d, *J*=6.57 Hz, 6 H) 2.11 (s, 3 H) 4.41 (quin, *J*=6.57 Hz, 1 H) 5.96 (s, 1 H) 6.83 (s, 1 H) 7.09 (ddd, *J*=8.02, 5.12, 3.03 Hz, 1 H) 7.40 (1 H) 7.52 - 7.61 (m, 2 H) 7.91 - 8.16 (m, 2 H) 8.55 (s, 1 H) 10.17 (brs, 1 H) 13.64 (brs, 1 H); HPLC Rt= 2.35 min, MS (ESI): [M+H]⁺ = 386.1.

Example 41b

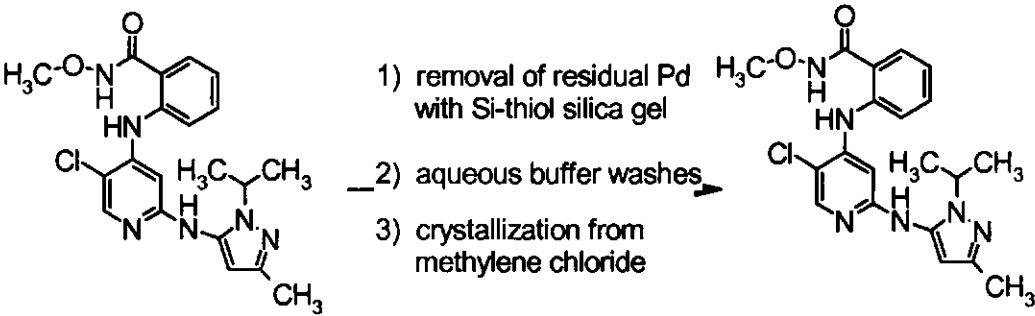
- 20 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-(methyloxy)benzamide



- To a solution of 2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzoic acid (67 g, 174 mmol) and 1-hydroxybenzotriazole (29.3 g, 191 mmol) in N,N-dimethylformamide (700 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (36.6 g, 191 mmol) and the solution was stirred for 30 minutes. O-Methylhydroxylamine hydrochloride (15.95 g, 191 mmol) was added and the solution stirred for additional 15 minutes, the cooled down to the 0° C and diisopropylethylamine (91 mL, 521 mmol) was added dropwise.

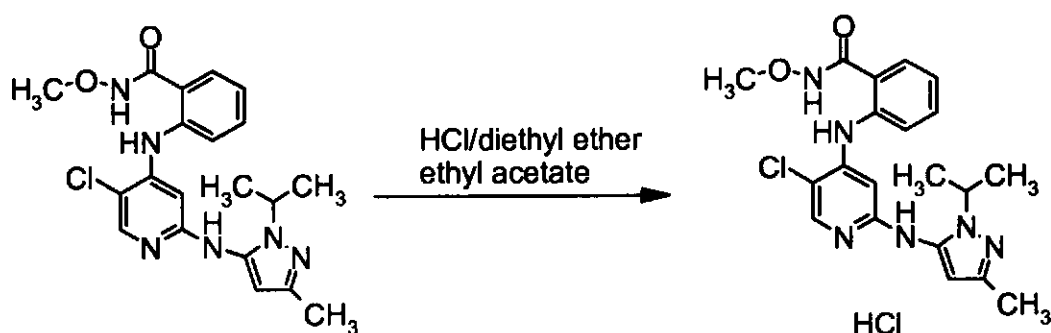
The reaction mixture was stirred overnight at the room temperature. Water (4000 mL) was added and the solution was acidified with acetic acid (20 mL). The solution was extracted 2 x 2 L of ethyl acetate. The organic was washed with water (1 L), brine, and dried over MgSO₄, filtered and evaporated. 2-[(5-Chloro-2-{{3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl}amino}-4-pyridinyl)amino]-N-(methoxy)benzamide (74 g, 164 mmol, 94 % yield, 92 % pure) was isolated as a yellow foam. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (d, *J*=6.57 Hz, 6 H) 2.10 (s, 3 H) 3.71 (s, 3 H) 4.39 (quin, *J*=6.51 Hz, 1 H) 5.93 (s, 1 H) 6.66 (s, 1 H) 7.08 - 7.19 (m, 1 H) 7.49 - 7.64 (m, 3 H) 7.98 (s, 1 H) 8.50 (s, 1 H) 9.50 (s, 1 H) 11.93 (s, 1 H).; HPLC Rt= 2.13 min, MS (ESI): [M+H]⁺ = 415.1.

Purification of Example 41a and 41b Products



2-[(5-Chloro-2-{{3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl}amino}-4-pyridinyl)amino]-N-(methoxy)benzamide (173.3 g, 63.5% w/w, 265.2 mmoles) was dissolved in ethyl acetate (3.50 L, 20 volumes) and heated to about 50° C. To this solution was added Si-thiol (functionalized silica gel) (87 g, 50% loading). The mixture was held at about 50 °C for 16-20 hours. It was then filtered off the Si-thiol silica gel. The filter cake was rinsed with ethyl acetate (2 x 200 mL each) and filtrates were combined. Then the combined filtrates were washed with 1 M aqueous ammonium formate at pH 9.4 (5 x 1 L each), washed with water, brine, and dried over magnesium sulfate. Dried EtOAc was filtered and stripped to dryness giving a yellow foam. It was dried at 50-55 °C for about 2 hours to a constant weight of 160 g. This material was slurried in methylene chloride (800 mL, 5 volumes), heated to reflux to afford a solution, and filtered. The solution was cooled to 20-25° C. The product crystallized upon cooling. After about 2 hours, the product was collected by filtration and rinsed with methylene chloride. The white solid was dried at 50-55° C for 14-16 hours to a constant weight. 2-[(5-Chloro-2-{{3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl}amino}-4-pyridinyl)amino]-N-(methoxy)benzamide (85.0 g, 204.9 mmoles, 77% overall yield) was isolated as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (d, *J*=6.57 Hz, 6 H) 2.10 (s, 3 H) 3.70 (s, 3 H) 4.39 (quin, *J*=6.57 Hz, 1 H) 5.92 (s, 1 H)

6.66 (s, 1 H) 7.02-7.24 (m, 1 H) 7.45-7.68 (m, 3 H) 7.98 (s, 1 H) 8.48 (s, 1 H) 9.49 (br. s, 1 H) 11.91 (s, 1 H). C18 HPLC RT = 6.2 minutes (99.0% purity). MS (ESI): 415.0 [M+H]⁺.

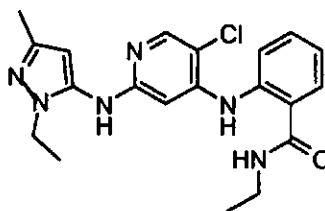


- 5 2-[(5-Chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-(methoxy)benzamide (235.2 g total weight, 228.0 g assayed content, 549.5 mmoles) was slurried in ethyl acetate (7.1 L, 30 volumes). The mixture was heated to about 50-55° C to afford a cloudy solution. The cloudy solution was filtered. To the filtered solution was added 2.0 M HCl in diethyl ether (210 g, 281 mL, 1.02 equiv.) over 15-20 minutes. Upon
- 10 HCl addition, a white slurry was observed. It was stirred at room temperature for about 16-20 hours. Product was collected by filtration and rinsed with ethyl acetate (2 x 500 mL each). The wet cake was dried at 50-55° C/<5 mm Hg for 16-20 hours to a constant weight. 2-[(5-Chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-(methoxy)benzamide, monohydrochloride, (245.9 g, 544.7 mmoles, 96% yield) was isolated as a
- 15 white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.32 (d, *J*=6.57 Hz, 6 H) 2.18 (s, 3 H) 3.70 (s, 3 H) 4.35-4.62 (m, 1 H) 6.12 (br. s, 1 H) 6.60 (br. s, 1 H) 7.19-7.41 (m, 1 H) 7.48-7.75 (m, 3 H) 8.09 (s, 1 H) 9.59-9.99 (m, 2 H) 11.98 (br. s, 1 H). C18 HPLC RT = 6.1 minutes (99.6% purity). MS (ESI): 414.8 [M+H]⁺.

20

Example 42

2-[(5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-ethylbenzamide

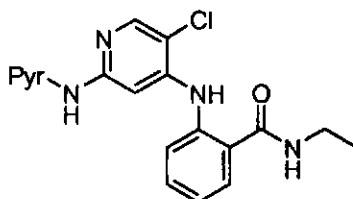


- A vessel was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-ethylbenzamide (100 mg, 0.322 mmol), 1-ethyl-3-methyl-1H-pyrazol-5-amine (60.5 mg, 0.484 mmol), cesium carbonate (315 mg, 0.967 mmol), 1,4-dioxane (5.0 mL), and THF (1.0 mL). The reaction mixture
- 25

was degassed by nitrogen for 10 min at which time ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (40.1 mg, 0.064 mmol) and palladium (II) acetate (7.24 mg, 0.032 mmol) in a minimum amount of 1,4-dioxane were added. The vessel was sealed and the reaction mixture was heated in microwave oven 160° C for 40 min. The resulting suspension was cooled to room temperature and filtered through celite. The filtrate was evaporated to dryness and the crude reaction mixture was purified by reverse-phase HPLC to give the title compound as a solid (45 mg, 30% yield); MS: $M(C_{20}H_{23}ClN_6O) = 398.89$, $(M+H)^+ = 399$, 401; ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.34 (s, 1 H) 7.94 (s, 1 H) 7.66 (br. s., 1 H) 7.51 (d, $J=7.8$ Hz, 1 H) 7.31 - 7.47 (m, 2 H) 6.96 - 7.17 (m, 1 H) 6.58 (s, 1 H) 6.19 (t, $J=5.2$ Hz, 1 H) 5.86 (s, 1H) 4.01 (q, $J=7.3$ Hz, 2 H) 3.42 - 3.62 (m, 2 H) 2.24 (s, 3 H) 1.37 (t, $J=7.3$ Hz, 3 H) 1.26 (t, $J=7.3$ Hz, 3 H).

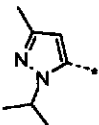
The 2-({5-chloro-2-(1H-pyrazol-5-yl)amino}-4-pyridinyl)amino)-N-ethylbenzamide compounds illustrated in Table 5 were prepared from 2-[(2,5-dichloro-4-pyridinyl)amino]-N-ethylbenzamide and amino-pyrazoles substantially according to the procedure of Example 42.

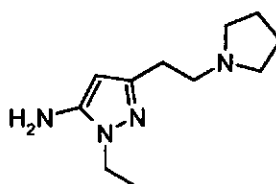
Table 5



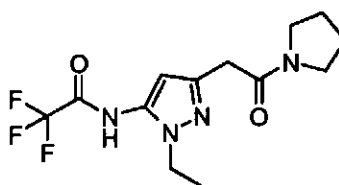
15

Ex	Name	Pyr	Data
43	2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-ethylbenzamide		LC-MS (ES) $m/z = 385$ ($M+H$) ⁺ ; ^1H NMR (400 MHz, MeOD) δ ppm 7.91 (s, 1 H) 7.67 (dd, $J=7.8$, 1.52 Hz, 1 H) 7.44 - 7.58 (m, 2 H) 7.14 - 7.24 (m, 1 H) 6.61 (s, 1 H) 5.98 (s, 1 H) 3.62 (s, 3 H) 3.37 - 3.46 (m, 2 H) 2.19 (s, 3 H) 1.21 (t, $J=7.3$ Hz, 3H)
44	2-({5-Chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-ethylbenzamide		LC-MS (ES) $m/z = 415$, 416 ($M+H$) ⁺ ; ^1H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 9.85 (s, 1 H) 8.00 (s, 1 H) 7.46 - 7.54 (m, 2 H) 7.33 - 7.44 (m, 2 H) 6.88 - 7.12 (m, 1 H) 6.72 (br. s., 1 H) 6.52 (s, 1 H) 5.93 - 6.17 (m, 2 H) 4.09 (q, $J=7.2$ Hz, 2 H) 3.38 - 3.57 (m, 2 H) 1.34 - 1.49 (m, 3 H) 1.26 (t, $J=7.3$ Hz, 3 H)

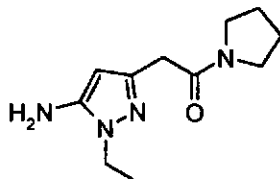
45	2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-ethylbenzamide		LC-MS (ES) $m/z = 413 (M+H)^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.04 (s, 1 H) 8.71 (t, $J=5.4$ Hz, 1 H) 8.48 (s, 1 H) 7.97 (s, 1 H) 7.71 (dd, $J=7.8, 1.26$ Hz, 1 H) 7.44 - 7.59 (m, 2 H) 7.04 - 7.19 (m, 1 H) 6.69 (s, 1 H) 5.93 (s, 1 H) 4.30 - 4.45 (m, 1H) 3.22 - 3.31 (m, 2 H) 2.10 (s, 3 H) 1.29 - 1.36 (d, $J=8.0$ Hz 6 H) 1.12 (t, $J=7.2$ Hz, 3 H)
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Intermediate 61-Ethyl-3-[2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-amine

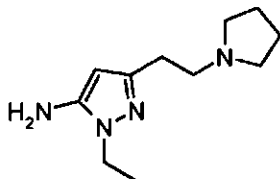
5 Int. 6a) N-{1-Ethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-yl]-2,2,2-trifluoroacetamide



- Pentafluorophenyl trifluoroacetate (497 mg, 1.773 mmol) was added dropwise to a stirred solution of (5-amino-1-ethyl-1H-pyrazol-3-yl) acetic acid (150 mg, 0.887 mmol) and pyridine (0.143 mL, 1.773 mmol) in DMF (3 mL). The reaction mixture was stirred for 15 min and pyrrolidine (0.220 mL, 2.66 mmol) was added. The reaction mixture was stirred at 65°C for 40 min. The mixture was cooled and quenched with water (5 mL) and extracted with EtOAc (3x). The extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified using RP-HPLC to give product (125 mg). MS: $(M+H)^+ = 318.8$. ^1H NMR (400 MHz, CHLOROFORM- d)
- 10 δ ppm 1.32 (t, $J = 7.2$ Hz, 3H), 1.87 - 2.06 (m, 4 H), 3.46 (t, $J = 6.8$ Hz, 2H), 3.53 (t, $J = 6.8$ Hz, 2H), 3.66 (s, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 5.30 (s, 1H).
- 15

Int. 6b) 1-ethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-amine

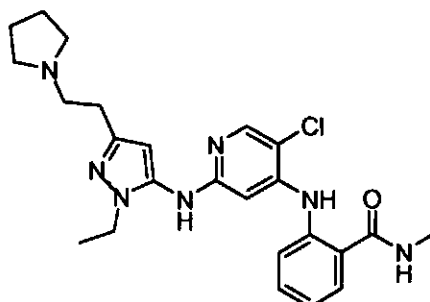
To a solution of N-{1-ethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-yl}-2,2,2-trifluoroacetamide (120 mg, 0.377 mmol) in methanol (1.5 mL) was added 2M HCl (1 mL, 0.377 mmol), and the reaction mixture was stirred at 50 °C for 2h and concentrated. The residue was
 5 neutralized using saturated NaHCO₃ solution and concentrated. The residue was dried under high vacuum to give 79 mg and used for next reaction without further purification. MS: (M+H)⁺=222.8. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.18 (t, J = 7.2 Hz, 3H), 1.70 – 1.85 (m, 4 H), 3.24 (t, J = 6.8 Hz, 2H), 3.31 (s, 2 H), 3.43 (t, J = 6.8 Hz, 2H), 3.78 (q, J = 7.2 Hz, 2H), 5.11
 10 (s, 1H).

Int. 6c) 1-ethyl-3-[2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-amine

To a solution of 1-ethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-amine (600 mg, 1.784 mmol) in tetrahydrofuran (8 mL) cooled with water-ice bath was added a solution of 2M
 15 LAH (1.0 mL, 2.00 mmol) solution dropwise, and the reaction mixture was stirred for 5h at rt and 30 min at 50 degree. The reaction mixture was carefully quenched with methanol followed by water and concentrated. The residue was washed with DCM/methanol 5 times. The extract was concentrated and the residue was purified using HPLC under the basic conditions to give 220 mg of product. MS: (M+H)⁺ = 208.7. ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.37 (t, J =
 20 7.2 Hz, 3H), 1.79 (m, 4H), 2.56 (m, 4H), 2.71 (m, 2H), 3.42 (m, 2H), 3.94 (q, J = 7.2 Hz, 2H), 5.40 (s, 1H).

Example 46

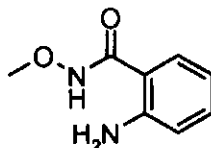
2-[[5-Chloro-2-({1-ethyl-3-[2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-yl}amino)-4-pyridinyl]amino]-N-methylbenzamide



- 5 To a 5-mL microwave tube were added 2-[(2,5-dichloro-4-pyridinyl)amino]-N-methylbenzamide (100 mg, 0.338 mmol), 1-ethyl-3-[2-(1-pyrrolidinyl)ethyl]-1H-pyrazol-5-amine (70.3 mg, 0.338 mmol), cesium carbonate (330 mg, 1.013 mmol), and 1,4-dioxane (2 mL), and the mixture was degassed by bubbling nitrogen through for 15 min. Palladium (II) acetate (3.79 mg, 0.017 mmol) and BINAP (21.03 mg, 0.034 mmol) were added, and the reaction mixture was
- 10 heated at 170 °C with stirring under microwave conditions for 40 min. The reaction mixture was filtered and concentrated. The residue was purified by using RP-HPLC under basic conditions (Gemini 5u C18(2) 110A, AXI. 50x30.00 mm 5 micron: 7.3-minute run, 47mL/min, 40%ACN/H₂O, 0.1%NH₄OH to 90% ACN/H₂O, 0.1% NH₄OH with UV detection at 254nm) to give the title compound (62 mg). MS: (M+H)⁺ = 468.1. ¹H NMR (400 MHz, DMSO-d₆) δ ppm
- 15 1.21 (t, J = 7.2 Hz, 3 H), 1.67 (m, 4H), 2.45 (m, 4), 2.60 (m, 4H), 2.77 (d, J = 4.0 Hz, 3H), 3.89 (q, J = 7.2 Hz, 2H), 6.03 (s, 1H), 6.74 (s, 1H), 7.11 (m, 1H), 7.49 (m, 1H), 7.54 (m, 1H), 7.71 (d, J = 7.2 Hz, 1H), 8.00 (s, 1H).

Intermediate 7

20 2-Amino-N-methoxy-benzamide



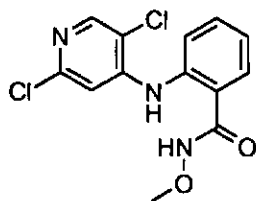
- To a mixture of isatoic anhydride (40 g, 245.39 mmol, 1 eq) and o-methyl hydroxylamine hydrochloride (30.55 g, 368.09 mmole, 1.5 eq) in EtOH:H₂O (9:1) (1000 mL) was added triethylamine (51.2 mL, 368.09 mmole, 1.5 eq) and resulting mixture was reflux for 4h. After
- 25 completion of reaction solvent was removed under reduced pressure and residue was diluted with water (500 mL), extracted with ethyl acetate (3x250 mL). Combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Solid compound so obtained was

purified by washing with diethyl ether and hexane to give the title compound as brown solid (20 g, 49%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 3.67 (s, 3H), 6.20-6.40 (brs, 2H), 6.44-6.53 (m, 1H), 6.70 (d, 1H, *J* = 7.76 Hz), 7.10-7.19 (m, 1H), 7.30 (d, 1H, *J* = 7.6 Hz), 11.40 (s, 1H). LC-MS [*M* + *H*]⁺ = 167.2.

5

Intermediate 8

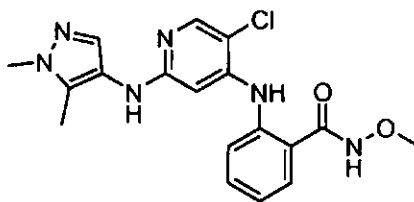
2-(2,5-Dichloropyridin-4-ylamino)-*N*-methoxy-benzamide (CR637-KS210635-027A1)



- 10 A mixture of 2,5-dichloro-4-iodo-pyridine (40 g, 146.5 mmole, 1 eq), 2-amino-*N*-methoxy-benzamide (24.32 g, 146.5 mmole, 1 eq) and K₃PO₄ (77.72 g 366.2mmole, 2.5 eq) in 1,4-dioxane (600 mL) was degassed with N₂ for 1h. To this were added Pd(OAc)₂ (0.657 g, 2.93 mmole, 0.02 eq), DPEPhos (6.31 g, 11.7 mmole, 0.08 eq) and again degassed for 15 min with N₂. The resulting mixture was stirred at 110°C for overnight. After completion of reaction, solid
- 15 material was collected by filtration, dissolved in water (500 mL) and extracted with ethyl acetate (5×200 mL). Combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Solid compound so obtained was purified by washing with hexane to give the title compound as yellowish solid (40 g, 53%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 3.63 (s, 3H), 7.06 (s, 1H), 7.15-7.22 (m, 1H), 7.48-7.57 (m, 2H), 7.66-7.67 (d, 1H, *J* = 7.48 Hz), 8.25 (s, 1H),
- 20 10.66-11.45 (brs, 1H). LC-MS [*M* + *H*]⁺ = 312.3.

Example 47

2-({5-Chloro-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl}amino)-*N*-(methyloxy)benzamide



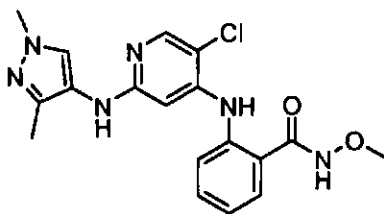
25

A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-*N*-(methyloxy)benzamide (200 mg, 0.64 mmol), 1,5-dimethyl-1*H*-pyrazol-4-amine (142 mg, 1.28 mmol), cesium carbonate (626 mg, 1.92 mmol) and dioxane/THF (3:1 ml). The reaction mixture

was degassed under nitrogen for 10 min and palladium (II) acetate (5.8 mg, 0.03 mmol) and BINAP (40 mg, 0.06 mmol) were added. The tube was sealed and the mixture was stirred in an oil bath at 150° C overnight. The dark brown solution was filtered thru celite and evaporated. It was dissolved in MeOH and filtered thru an Acrodisc (Pall Corporation; www.pall.com) and further
 5 purified on preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). The dark brown oil residue was dissolved in DMF and water was slowly added. A tan precipitate crashed out and was filtered off and dried under vacuum at 40° C for 2 hrs to afford the desired product (18 mg, 7.3 %) as a tan solid. LC-MS $[M+H]^+ = 387.1, 389.1$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.91 (br. s., 1 H) 9.41 (br. s., 1 H) 7.85 - 7.98 (m, 2 H) 7.49 - 7.59 (m, 3 H)
 10 7.42 (br. s., 1 H) 7.07 - 7.13 (m, 1 H) 6.50 (br. s., 1 H) 3.69 (d, $J=10.36$ Hz, 6 H) 2.11 (s, 3 H).

Example 48

2-((5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl)amino)-N-(methoxy)benzamide

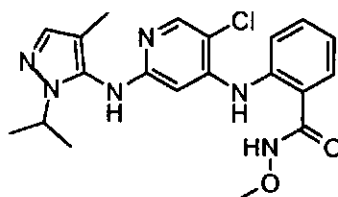


15

A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methoxy)benzamide (250 mg, 0.8 mmol), 1,3-dimethyl-1H-pyrazol-4-amine (187 mg, 1.68 mmol), cesium carbonate (783 mg, 2.4 mmol) and dioxane/THF (3:1 ml). The reaction mixture was degassed under nitrogen for 10 min and palladium (II) acetate (9 mg, 0.04 mmol) and BINAP
 20 (50 mg, 0.08 mmol) were added. The mixture was stirred in a microwave at 140°C for 40 min. It was evaporated and the residue dissolved in MeOH was filtered thru celite and thru an Acrodisc and purified further using preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). Fractions were combined and evaporated. Ether was added to the residue and a tan precipitate crashed out. It was filtered off and dried under vacuum at 40° C for 2 days to afford the
 25 desired product (55 mg, 18%) as a tan solid. LC-MS (ES) $m/z = 387.1, [M+H]^+ = 389.1$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br. s., 1 H) 9.51 (br. s., 1 H) 8.03 (s, 1 H) 7.96 (s, 1 H) 7.82 (s, 1 H) 7.51 - 7.61 (m, 3 H) 7.07 - 7.15 (m, 1 H) 6.68 (s, 1 H) 3.70 (d, $J=4.29$ Hz, 6 H) 2.07 (s, 3 H).

Example 49

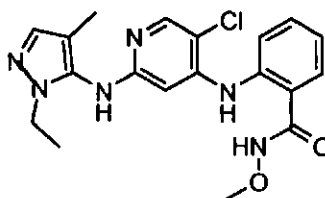
2-[(5-Chloro-2-[(4-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-(methyloxy)benzamide



- 5 A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide (100 mg, 0.32 mmol), 4-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (93.6 mg, 0.67 mmol), cesium carbonate (312.8 mg, 0.96 mmol) and DMF (5 mL). The reaction mixture was degassed under nitrogen for 10 min and palladium (II) acetate (3.6 mg, 0.016 mmol) and BINAP (19.9 mg, 0.032 mmol) were added. The reaction mixture was heated in an oil bath for 6 hours and then in a microwave at 150° C for 40 min. The solvent was evaporated and the residue dissolved in MeOH. It was filtered thru celite and thru an Acrodisc to be purified on preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). Fractions were combined and evaporated. The brown oil residue was diluted in DMF and water was added. A precipitate crashed out. It was filtered and dried under vacuum at 40° C for 6 hrs. LC-MS [M+H]⁺ = 415.1. ¹H
- 15 NMR (400 MHz, DMSO-*d*₆) δ ppm 11.93 (s, 1 H) 9.48 (br. s., 1 H) 8.23 (s, 1 H) 7.93 (s, 1 H) 7.58 (d, *J*=7.83 Hz, 1 H) 7.50 (d, *J*=3.79 Hz, 2 H) 7.24 (s, 1 H) 7.12 (dt, *J*=7.83, 4.17 Hz, 1 H) 6.40 (br. s., 1 H) 4.33 (dt, *J*=13.14, 6.57 Hz, 1 H) 3.71 (s, 3 H) 1.78 (s, 3 H) 1.26 (d, *J*=6.57 Hz, 6 H).

Example 50

20 2-[(5-Chloro-2-[(1-ethyl-4-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino]-N-(methyloxy)benzamide



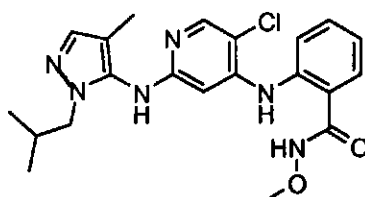
- A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methyloxy)benzamide (300 mg, 0.96 mmol), 1-ethyl-4-methyl-1H-pyrazol-5-amine (253 mg, 2.01 mmol), cesium carbonate (939 mg, 2.88 mmol) and DMF (7 ml). The reaction mixture was degassed under nitrogen for 10 min and palladium (II) acetate (10.8 mg, 0.05 mmol) and BINAP (59.8 mg, 0.096 mmol) were added. The reaction mixture was heated in an oil bath at 90° C for 5 hrs and then in a microwave at 150° C for 50 min. It was evaporated and the residue was dissolved

in MeOH, filtered thru celite and thru an Acrodisc and purified further on preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). Fractions were combined and evaporated. The brown oil residue was diluted in DMF and water was added. A precipitate crashed out. It was filtered off and dried under vacuum at 40° C for 5 hrs. LC-MS $[M+H]^+ = 401.1$. 1H

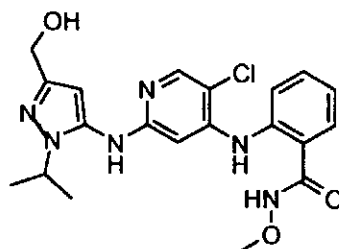
- 5 NMR (400 MHz, DMSO- d_6) δ ppm 11.92 (s, 1 H) 9.48 (br. s., 1 H) 8.27 (s, 1 H) 7.94 (s, 1 H) 7.59 (d, $J=7.58$ Hz, 1 H) 7.51 (d, $J=3.54$ Hz, 2 H) 7.22 (s, 1 H) 7.09 - 7.16 (m, 1 H) 6.40 (s, 1 H) 3.85 (q, $J=7.33$ Hz, 2 H) 3.71 (s, 3 H) 1.79 (s, 3 H) 1.21 (t, $J=7.20$ Hz, 3 H).

Example 51

- 10 2-[(5-Chloro-2-{[4-methyl-1-(2-methylpropyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-(methoxy)benzamide



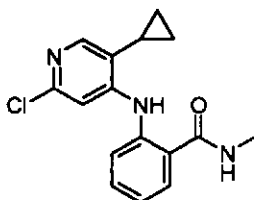
- A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methoxy)benzamide (300 mg, 0.96 mmol), 4-methyl-1-(2-methylpropyl)-1H-pyrazol-5-amine (309 mg, 2.01 mmol), cesium carbonate (939 mg, 2.88 mmol) and DMF (5 ml). The reaction mixture was degassed under nitrogen for 10 min, and palladium (II) acetate (10.8 mg, 0.05 mmol) and BINAP (59.8 mg, 0.096 mmol) were added. The reaction mixture was heated in an oil bath at 90° C for 5 hrs and then in a microwave at 150° C for 40 min. Solvent was evaporated and the residue was dissolved in MeOH, filtered thru celite and thru an Acrodisc and purified further using preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). Fractions were combined and evaporated. The brown oil residue was diluted in DMF and water was added. A precipitate crashed out. It was filtered off and dried under vacuum at 40° C for 5 hrs. LC-MS $[M+H]^+ = 429.1$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (s, 1 H) 9.48 (br. s., 1 H) 8.26 (s, 1 H) 7.94 (s, 1 H) 7.58 (d, $J=7.33$ Hz, 1 H) 7.44 - 7.51 (m, 2 H) 7.23 (s, 1 H) 7.08 - 7.16 (m, 1 H) 6.38 (s, 1 H) 3.70 (s, 3 H) 3.65 (d, $J=7.33$ Hz, 2 H) 2.03 (dt, $J=13.71, 6.92$ Hz, 1 H) 1.77 (s, 3 H) 0.75 (d, $J=6.57$ Hz, 6 H).

Example 522-[(5-Chloro-2-[[3-(hydroxymethyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-N-(methoxy)benzamide

5

A microwave tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-N-(methoxy)benzamide (188 mg, 0.602 mmol), [5-amino-1-(1-methylethyl)-1H-pyrazol-3-yl]methanol (140 mg, 0.90 mmol), cesium carbonate (589 mg, 1.81 mmol) and DMF (5 ml). The reaction mixture was degassed under nitrogen for 10 min and palladium (II) acetate (6.8 mg, 0.03 mmol) and BINAP (37.5 mg, 0.06 mmol) were added. The reaction mixture was heated in an oil bath at 90° C for 5 hrs and then in a microwave at 150° C for 40 min. It was evaporated and the residue was dissolved in MeOH, filtered thru celite and thru an Acrodisc and purified further using preparative Agilent HPLC (5 to 95% water:acetonitrile with 0.1% formic acid). Fractions were combined and evaporated. EtOAc was added to the brown oil residue. Then the mixture was heated and hexane was added dropwise. A light yellow precipitate crashed out upon sonication. It was filtered off and dried under vacuum at 40° C for 12 hrs. LC-MS $[M+H]^+ = 431.2$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br. s., 1 H) 9.54 (br. s., 1 H) 8.54 (s, 1 H) 7.96 - 8.01 (m, 1 H) 7.52 - 7.62 (m, 3 H) 7.11 - 7.16 (m, 1 H) 6.70 (s, 1 H) 6.10 (s, 1 H) 4.95 (t, $J=5.81$ Hz, 1 H) 4.43 (dt, $J=13.14, 6.57$ Hz, 1 H) 4.33 (d, $J=5.56$ Hz, 2 H) 3.71 (s, 3 H) 1.29 (d, $J=6.57$ Hz, 6 H).

20

Intermediate 92-(2-Chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methyl-benzamide 1

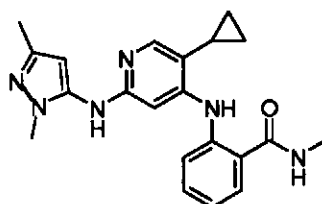
A solution of cyclopropylboronic acid (0.38 g, 4.40 mmole, 1.5 eq) in toluene (100 mL) was degassed with N_2 at 50° C for 15 min. To this was added $Pd(PPh_3)_4$ (0.17 g, 0.15 mmole, 0.05 eq) and 2-(5-bromo-2-chloro-pyridin-4-ylamino)-N-methyl-benzamide (1 g, 2.93 mmole, 1 eq) and the resulting reaction mixture was again degassed for 30 min. To this a degassed solution K_3PO_4

(2.49 g, 11.72 mmole, 4 eq) in H₂O (4 mL) was added in one portion and the resulting reaction mixture was refluxed for overnight. Solvent was removed under reduced pressure and the residue was diluted with water (100 mL) and then extracted with DCM (3×75 mL). Combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield crude product. Crude compound was purified by column chromatography over silica gel (60-120 mesh) using 0.5% MeOH-DCM as the eluant to give the title compound as a pale yellow solid (0.480 g, 54%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.60-0.70 (m, 2H), 0.95-1.05 (m, 2H), 1.60-1.71 (m, 1H), 2.76 (d, 3H, *J* = 4.48 Hz), 7.09 (s, 1H), 7.10-7.18 (m, 1H), 7.49-7.60 (m, 2H), 7.68-7.70 (d, 1H, *J* = 7.64 Hz), 7.93 (s, 1H), 8.60-8.70 (m, 1H), 10.22 (s, 1H). LC-MS [M+H]⁺ = 302.0.

10

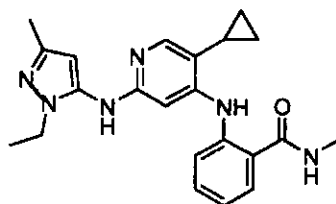
Example 53

2-[5-Cyclopropyl-2-(2,5-dimethyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methyl-benzamide



To a 10 mL microwave tube were added 2-(2-chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methyl-benzamide (0.075 g, 0.25 mmol, 1eq), 2,5-dimethyl-2H-pyrazol-3-ylamine (0.030 g, 0.27 mmol, 1.1 eq), Cs₂CO₃ (0.23g, 0.70 mmol, 2.8 eq) and 1,4-dioxane (4 mL) and resulting mixture was degassed with N₂ for 30 minutes. To this was added Pd₂(dba)₃ (0.008 g, 0.007 mmol, 0.03 eq) and xanthphos (0.009 g, 0.014 mmol, 0.06 eq) and reaction mixture was degassed again with N₂ for another 15 minutes. The resulting reaction mixture was irradiated in a CEM microwave at 110° C and 150 W for 40 min. The progress of reaction was monitored by LCMS. After completion of reaction, Cs₂CO₃ was removed by filtration and the filtrate was concentrated under reduced pressure to give a crude product. The crude compound was purified by column chromatography over neutral alumina using 0.1% MeOH-DCM as the eluant. Solid compound so obtained was washed with diethyl ether and pentane to give the title compound as a yellowish solid (16 mg, 17%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.52-0.59 (m, 2H), 0.89-0.99 (m, 2H), 1.52-1.62 (m, 1H), 2.05 (s, 3H), 2.76-2.77 (d, 3H, *J* = 4.44 Hz), 3.52 (s, 3H), 5.96 (s, 1H), 6.69 (s, 1H), 7.01-7.05 (t, 1H, *J* = 7.48 Hz), 7.42-7.45 (m, 1H), 7.51-7.60 (m, 1H), 7.64-7.66 (d, 1H, *J* = 7.32 Hz), 7.72 (s, 1H), 8.37 (s, 1H), 8.55-8.65 (brs, 1H), 9.96 (s, 1H). LC-MS [M+H]⁺ = 377.2.

30

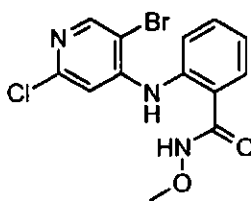
Example 542-[5-Cyclopropyl-2-(2-ethyl-5-methyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methylbenzamide

5 To a 10 mL microwave tube were added 2-(2-chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methyl-benzamide (0.075 g, 0.25 mmol, 1eq), 2-ethyl-5-methyl-2H-pyrazol-3-ylamine (0.035 g, 0.27 mmol, 1.1 eq), Cs₂CO₃ (0.23g, 0.70 mmol, 2.8 eq) and 1,4-dioxane (3 mL) and the resulting mixture was degassed with N₂ for 30 minutes. To this mixture was added Pd₂(dba)₃ (0.008 g, 0.007 mmol, 0.03 eq) and xanthphos (0.009 g, 0.015 mmol, 0.06 eq) and this mixture was degassed again

10 with N₂ for another 10 minutes. The resulting reaction mixture was irradiated in a CEM microwave at 110 °C and 150 W for 45 min. The progress of the reaction was monitored by LCMS. After completion of the reaction, Cs₂CO₃ was removed by filtration and the filtrate was concentrated under reduced pressure to give a crude product. It was purified using column chromatography over neutral alumina using 0.2% MeOH-DCM as the eluant. The solid compound

15 so obtained was washed with diethyl ether and hexane to give the title compound as a white solid (20 mg, 20%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.50-0.62 (m, 2H), 0.88-0.99 (m, 2H), 1.15-1.28 (m, 3 H), 1.55-1.65 (m, 1H), 2.07 (s, 3H), 2.76-2.77 (d, 3H, *J* = 4.36 Hz), 3.82-3.95 (m, 2H), 5.95 (s, 1H), 6.68 (s, 1H), 6.99-7.10 (m, 1H), 7.42-7.50 (m, 1H), 7.50-7.55 (m, 1H) 7.64-7.66 (d, 1H, *J* = 7.6 Hz), 7.71 (s, 1H), 8.30 (s, 1H), 8.55-8.70 (brs, 1H), 9.95 (s, 1H). LC-MS [M+H]⁺ = 391.4.

20

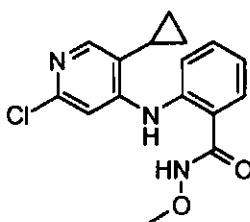
Intermediate 102-(5-Bromo-2-chloro-pyridin-4-ylamino)-N-methoxy-benzamide

25 A mixture of 5-bromo-2-chloro-4-iodo-pyridine (5 g, 15.72 mmole, 1 eq), 2-amino-N-methoxy-benzamide (2.61 g, 15.72 mmole, 1 eq) and K₃PO₄ (8.34 g, 39.3 mmole, 2.5 eq), and 1,4-dioxane (30 mL) was degassed with N₂ for 1 h. To this was added DPEPhos (0.67 g, 1.25 mmole, 0.08 eq) and Pd(OAc)₂ (0.07 g, 0.31 mmole, 0.02 eq) and this mixture was degassed again with N₂ for 30 min. The resulting mixture was refluxed for overnight. After completion of reaction, solvent

was removed under reduced pressure and residue was diluted with water (100 mL) and extracted with 5% MeOH-DCM (3×100 mL). Combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude compound. It was purified by column chromatography over silica gel (60-120 mesh) using 20% Ethyl acetate-hexane as the eluant to yield the title compound as off white solid (3.5 g, 62%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 3.56 (s, 3H), 6.88-6.98 (m, 1H), 7.08 (s, 1H), 7.17-7.25 (m, 1H), 7.26-7.35 (m, 1H), 7.82-7.90 (m, 1H), 8.23 (s, 1H), 12.86 (brs, 1H). LC-MS [M+H]⁺ = 356.30.

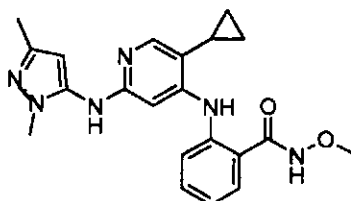
Intermediate 11

10 2-(2-Chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methoxy-benzamide



In a sealable tube toluene (50 mL) was degassed with N₂ at 50 °C for 15 min and to this 2-(5-bromo-2-chloro-pyridin-4-ylamino)-N-methoxy-benzamide (1.5 g, 4.21 mmole, 1 eq), cyclopropylboronic acid (1.4 g, 16.85 mmole, 4 eq) and Pd(PPh₃)₄ (0.24 g, 0.21 mmole, 0.05 eq) were added and resulting mixture was degassed for 30 min. To this NaBr (0.44 g, 4.33 mmole, 1.03 eq) and a solution of KF (0.8 g, 13.90 mmole, 3.3 eq) in H₂O (3 mL) were added; again degassed with N₂ for 15 min. The tube was sealed and the resulting mixture was heated at 100 °C for 24 h. After completion of reaction, reaction mixture was allowed to cool at room temperature, poured into water (100 mL) and extracted with toluene (2×50 mL). Combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude compound was purified by washing with 0.5% DCM-Et₂O to give titled compound as pale yellow solid (0.7 g, 53%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.57-0.72 (m, 2H), 0.97-1.10 (m, 2H), 1.62-1.75 (m, 1H), 3.68 (s, 3H), 7.02 (s, 1H), 7.11-7.20 (m, 1H), 7.51-7.67 (m, 3H), 7.94 (s, 1H), 9.62 (s, 1H), 11.92 (brs, 1H). LC-MS [M+H]⁺ = 318.2.

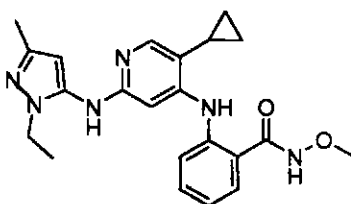
41

Example 552-[5-Cyclopropyl-2-(2,5-dimethyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methoxy-benzamide

- 5 To a 10 mL microwave tube were added 2-(2-chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methoxy-benzamide (0.075 g, 0.24 mmol, 1eq), 2,5-dimethyl-2H-pyrazol-3-ylamine (0.05 g, 0.47 mmol, 2 eq), Cs₂CO₃ (0.23 g, 0.71 mmol, 3 eq), and 1,4-dioxane (3 mL). The resulting mixture was degassed with N₂ for 15 min. To this was added Pd₂(dba)₃ (0.015 g, 0.014 mmol, 0.06 eq) and xanthphos (0.03 g, 0.06 mmol, 0.25 eq) and the mixture was again degassed with N₂ for 30 min.
- 10 The resulting mixture was irradiated in a CEM microwave at 120°C, 150 W for 35 min. After completion of reaction, solvent was removed under reduced pressure and crude compound was purified using column chromatography over silica gel (100-200 mesh) using 1% MeOH-DCM as the eluant followed by prep HPLC. Solid compound so obtained was washed with diethyl ether and pentane to give the title compound as an off white solid (11 mg, 12%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.52-0.60(m, 2H), 0.82-1.00 (m, 2H), 1.50-1.62 (m, 1H), 2.05 (s, 3H), 3.52 (s, 3H), 3.70 (s, 3H), 5.96 (s, 1H), 6.67 (s, 1H), 6.98-7.10 (m, 1H), 7.40-7.60 (m, 3H), 7.73 (s, 1H), 8.39 (s, 1H), 9.46 (s, 1H), 11.88 (brs, 1H). LC-MS [M+H]⁺ = 393.4.
- 15

Example 56

20 2-[5-Cyclopropyl-2-(2-ethyl-5-methyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methoxy-benzamide

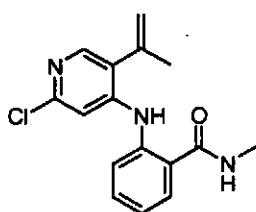


- To a 10 mL microwave tube were added 2-(2-chloro-5-cyclopropyl-pyridin-4-ylamino)-N-methoxy-benzamide (0.075 g, 0.24 mmol, 1eq), 2-ethyl-5-methyl-2H-pyrazol-3-ylamine (0.05 g, 0.36 mmol, 1.5 eq), Cs₂CO₃ (0.23 g, 0.71 mmol, 3 eq), and 1,4-dioxane (3 mL) and the resulting mixture was degassed with N₂ for 15 min. To this was added Pd₂(dba)₃ (0.014 g, 0.014 mmol, 0.06 eq) and xanthphos (0.03 g, 0.06 mmol, 0.25 eq) and this mixture was again degassed with N₂ for another 10 min. The resulting mixture was irradiated in a CEM microwave at 120 °C, 150 W for
- 25

35 min. After the reaction was finished solvent was removed under reduced pressure and crude product was purified by column chromatography over silica gel (100-200 mesh) using 1% MeOH-DCM as the eluant followed by washing with diethyl ether and pentane and DCM to give the title compound as an off white solid (5 mg, 5%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 0.50-0.60(m, 2H), 0.88-1.00 (m, 2H), 1.15-1.27 (m, 3H), 1.55-1.65 (m, 1H), 2.07 (s, 3H), 3.70 (s, 3H), 3.80-3.95 (m, 2H), 5.95 (s, 1H), 6.64 (s, 1H), 6.90-7.10 (m, 1H), 7.40-7.60 (m, 3H), 7.72 (s, 1H), 8.34 (s, 1H), 9.47 (s, 1H), 11.88 (brs, 1H). LC-MS [M+H]⁺ = 407.3.

Intermediate 12

10 2-(2-Chloro-5-isopropenyl-pyridin-4-ylamino)-N-methyl-benzamide

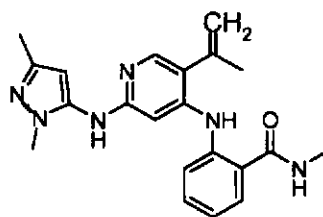


In a tube a solution of isopropenylboronic acid pinacol ester (3.31 mL, 17.6 mmole, 3 eq) in toluene (200 mL) was degassed with N₂ at 50° C for 15 min. To this was added Pd(PPh₃)₄ (0.68 g, 0.59 mmole, 0.1 eq) and 2-(5-bromo-2-chloro-pyridin-4-ylamino)-N-methyl-benzamide (2 g, 5.87 mmole, 1 eq). This mixture was again degassed with N₂ for 30 min. A degassed solution of K₃PO₄ (4.98 g, 23.48 mmole, 4 eq) in H₂O (8 mL) was added to the above mixture in one portion and the resulting mixture was heated at 110° C for overnight. After completion of the reaction, it was allowed to cool to room temperature and solvent was removed under reduced pressure to yield crude product. It was purified by column chromatography over silica gel (60-120 mesh) using 0.5% MeOH-DCM as the eluant to give the title compound as an off white solid (0.8 g, 45%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 2.06 (s, 3H), 2.73-2.74 (d, 3H, *J* = 4.52 Hz), 5.14 (s, 1H), 5.46 (s, 1H), 7.04-7.15 (m, 2H), 7.45-7.60 (m, 2H), 7.64-7.71 (m, 1H), 7.96 (s, 1H), 8.60-8.72 (brs, 1H), 9.87 (s, 1H). LC-MS [M+H]⁺ = 302.2.

25

Example 57

2-[2-(2,5-Dimethyl-2H-pyrazol-3-ylamino)-5-isopropenyl-pyridin-4-ylamino]-N-methyl-benzamide

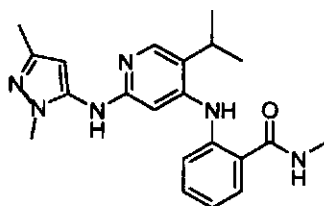


To a 10 mL microwave tube was added 2-(2-chloro-5-isopropenyl-pyridin-4-ylamino)-*N*-methyl-benzamide (0.075 g, 0.25 mmol, 1eq), 2,5-dimethyl-2*H*-pyrazol-3-ylamine (0.055 g, 0.50 mmol, 2 eq), Cs₂CO₃ (0.24 g, 0.74 mmol, 3 eq) and 1,4-dioxane (3 mL). The resulting mixture was degassed with N₂ for 30 minutes. Then Pd(OAc)₂ (0.015 g, 0.07 mmol, 0.27 eq) and BINAP (0.046 g, 0.074 mmol, 0.3 eq) were added and the mixture degassed again with N₂ for another 10 minutes. The resulting reaction mixture was irradiated in a CEM microwave at 110°C and 150 W for 45 min. The progress of the reaction was monitored by LCMS. After it was complete, Cs₂CO₃ was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography over neutral alumina using 0.2% MeOH-DCM as the eluant. This gave the title compound as an off white solid (180 mg, 48%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 2.02-2.10 (m, 6H), 2.73-2.74 (d, 3H, *J* = 4.48 Hz), 3.53 (s, 3H), 5.05 (s, 1H), 5.31 (s, 1H), 5.97 (s, 1H), 6.67 (s, 1H), 6.90-7.05 (m, 1H), 7.4-7.55 (m, 2H), 7.61-7.63 (d, 1H, *J* = 7.04 Hz), 7.76 (s, 1H), 8.48 (s, 1H), 8.54-8.67 (brs, 1H), 9.61 (s, 1H). LC-MS [M+H]⁺ = 377.4.

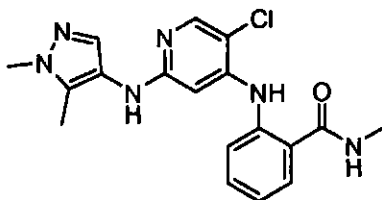
15

Example 58

2-[2-(2,5-Dimethyl-2*H*-pyrazol-3-ylamino)-5-isopropenyl-pyridin-4-ylamino]-*N*-methyl-benzamide

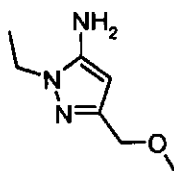


A solution of 2-[2-(2,5-dimethyl-2*H*-pyrazol-3-ylamino)-5-isopropenyl-pyridin-4-ylamino]-*N*-methyl-benzamide (0.13 g, 0.345 mmole, 1 eq) in ethanol (10 mL) was degassed with N₂ and to this PtO₂ (0.012 g, 0.052 mmole, 0.15 eq) was added. The resulting mixture was stirred at room temperature under H₂ atmosphere with balloon pressure for 10 h. After completion of the reaction, it was filtered through a celite bed which was then washed with ethanol (10 mL). The filtrate was evaporated under reduced pressure to give a solid residue which was purified by washing with diethyl ether to give the title compound as a gray solid (80 mg, 61%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 1.24-1.26 (d, 6H, *J* = 6.76 Hz), 2.05 (s, 3H), 2.75-2.76 (d, 3H, *J* = 4.48 Hz), 2.89-3.10 (m, 1H), 3.53 (s, 3H), 5.96 (s, 1H), 6.67 (s, 1H), 6.85-7.10 (m, 1H), 7.40-7.50 (m, 2H), 7.65-7.67 (d, 1H, *J* = 7.76 Hz), 7.86 (s, 1H), 8.36 (s, 1H), 8.60-8.70 (brs, 1H), 9.89 (s, 1H). LC-MS [M+H]⁺ = 379.2.

Example 592-({5-Chloro-2-[(1,5-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide

To a 10 mL scalable tube was added 2-[(2,5-dichloro-4-pyridinyl)amino]-N-methylbenzamide (95 mg, 0.321 mmol), 1,5-dimethyl-1H-pyrazol-4-amine (35.7 mg, 0.321 mmol), BINAP (20 mg, 0.032 mmol), cesium carbonate (314 mg, 0.964 mmol), and palladium(II) acetate (7.21 mg, 0.032 mmol) in 1,4-dioxane (5 mL). The reaction vessel was sealed and heated at 150° C for 1 hr. The reaction mixture was purified using a prep HPLC (0.1% formic acid, 5 to 95% water:acetonitrile). Fractions were combined and evaporated. 2-({5-Chloro-2-[(1,5-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide (16 mg, 0.037 mmol, 11.38 % yield) was isolated as yellow oil

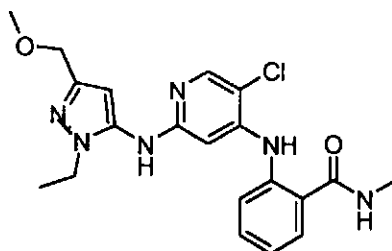
LCMS (M+H)⁺ = 371.1; ¹H NMR (400 MHz, MeOD) δ ppm 2.17 (s, 3 H) 2.91 (s, 3 H) 3.78 (s, 3 H) 6.47 (s, 1 H) 7.13 - 7.24 (m, 1 H) 7.40 (s, 1 H) 7.46 - 7.57 (m, 2 H) 7.67 (dd, J=7.83, 1.26 Hz, 1 H) 7.82 (s, 1 H).

Example 602-({5-Chloro-2-[(1-ethyl-3-[(methyloxy)methyl]-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide60a) 1-Ethyl-3-[(methyloxy)methyl]-1H-pyrazol-5-amine

To a 25 mL round bottom was added 4-(methyloxy)-3-oxobutanenitrile (500 mg, 4.42 mmol), ethyl hydrazine (655 mg, 4.42 mmol), and 2 M HCl (2.210 mL, 4.42 mmol) in ethanol (10 mL). The reaction mixture was stirred at the room temperature overnight. The reaction mixture was then evaporated and partitioned between 20 mL of ethyl acetate and 20 mL of 1 M Na₂CO₃. The organic layer was washed with brine, filtered and evaporated to obtain 1-ethyl-3-[(methyloxy)methyl]-1H-pyrazol-5-amine (450 mg, 2.465 mmol, 55.8 % yield) as a yellow oil. The product was used in the next step without further purification. LCMS (M+H)⁺ = 156.1; ¹H

NMR (400 MHz, DMSO- d_6) δ ppm 1.20 (t, $J=7.20$ Hz, 3 H) 3.19 (s, 3 H) 3.82 (q, $J=7.33$ Hz, 2 H) 4.11 (s, 2 H) 5.11 (s, 2 H) 5.22 (s, 1 H).

60b) 2-([5-chloro-2-([1-ethyl-3-[(methyloxy)methyl]-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino)-N-methylbenzamide



5

The title compound was prepared substantially as described in Example 59 except using 1-ethyl-3-[(methyloxy)methyl]-1H-pyrazol-5-amine instead of 5-amino-1-methyl-1H-pyrazole.

LCMS (M+H)⁺ = 415.1(M+H); ¹H NMR (400 MHz, DMSO- d_6) δ ppm 1.24 (t, $J=7.20$ Hz, 3 H) 2.78 (d, $J=4.55$ Hz, 3 H) 3.23 (s, 3 H) 3.95 (q, $J=7.07$ Hz, 2 H) 4.25 (s, 2 H) 6.20 (s, 1 H) 6.77 (s, 1 H) 7.05 - 7.16 (m, 1 H) 7.44 - 7.60 (m, 2 H) 7.70 (dd, $J=7.83, 1.26$ Hz, 1 H) 8.01 (s, 1 H) 8.63 (s, 1 H) 8.69 (q, $J=4.29$ Hz, 1 H) 10.12 (s, 1 H).

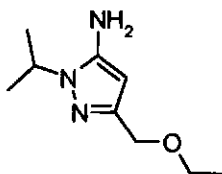
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Example 61

2-([5-Chloro-2-([3-[(ethyloxy)methyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino)-N-methylbenzamide

15

61a) 3-[(Ethyloxy)methyl]-1-(1-methylethyl)-1H-pyrazol-5-amine



To a 25 mL round bottom was added 4-(ethyloxy)-3-oxobutanenitrile (550 mg, 4.33 mmol), isopropyl hydrazine hydrochloride (478 mg, 4.33 mmol), and HCl (2.163 mL, 4.33 mmol) in Ethanol (10 mL). The reaction mixture was stirred at the room temperature overnight. The reaction mixture was then evaporated, and partitioned between 20 mL of ethyl acetate and 20 mL of 1 M Na₂CO₃. The organic layer was washed with brine, filtered and evaporated. 3-

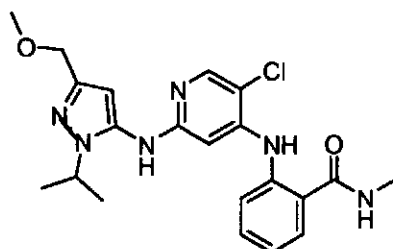
20

[(Ethyloxy)methyl]-1-(1-methylethyl)-1H-pyrazol-5-amine (520 mg, 2.84 mmol, 65.6 % yield) was isolated as yellow oil. The product was used in the next step without further purification. ¹H

25

NMR (400 MHz, DMSO- d_6) δ ppm 1.09 (t, $J=7.07$ Hz, 3 H) 1.26 (d, $J=6.57$ Hz, 6 H) 3.40 (q, $J=6.91$ Hz, 2 H) 4.16 (s, 2 H) 4.32 (quin, $J=6.57$ Hz, 1 H) 5.06 (s, 2 H) 5.22 (s, 1 H)

61b) 2-[(5-Chloro-2-{[3-[(ethyloxy)methyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-methylbenzamide



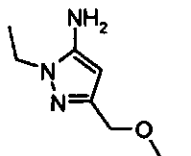
The title compound was prepared substantially as described in Example 59 except using 3-
 5 [(ethyloxy)methyl]-1-(1-methylethyl)-1H-pyrazol-5-amine instead of 5-amino-1-methyl-1H-
 pyrazole. LCMS (ES) $m/z = 443.1$ (M+H); ^1H NMR (400 MHz, MeOD) δ ppm 1.21 (t, $J=7.07$
 Hz, 3 H) 1.40 (d, $J=6.82$ Hz, 6 H) 2.91 (s, 3 H) 3.56 (q, $J=6.91$ Hz, 2 H) 4.45 (s, 2 H) 4.53 (quin,
 $J=6.69$ Hz, 1 H) 6.17 (s, 1 H) 6.60 (s, 1 H) 7.05 - 7.18 (m, 1 H) 7.40 - 7.56 (m, 2 H) 7.62 - 7.70 (m,
 1 H) 7.92 (s, 1 H)

10

Example 62

2-[(5-Chloro-2-{[1-ethyl-3-[(ethyloxy)methyl]-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-methylbenzamide

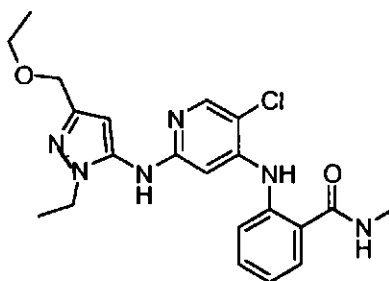
62a) 1-Ethyl-3-[(ethyloxy)methyl]-1H-pyrazol-5-amine



15

To a 25 mL round bottom was added 4-(ethyloxy)-3-oxobutanenitrile (550 mg, 4.33
 mmol), ethyl hydrazine oxalate (641 mg, 4.33 mmol), and HCl (2.163 mL, 4.33 mmol) in ethanol
 (10 mL). The reaction mixture was stirred at the room temperature overnight. The reaction mixture
 was then evaporated, and partitioned between 20 mL of ethyl acetate and 20 mL of 1 M Na_2CO_3 .
 20 The organic layer was washed with brine, filtered and evaporated. 1-Ethyl-3-[(ethyloxy)methyl]-
 1H-pyrazol-5-amine (420 mg, 2.234 mmol, 51.6 % yield) was isolated as yellow oil. The product
 was used in the next step without further purification. LCMS (M+H) $^+ = 170.1$ (M+H); ^1H NMR
 (400 MHz, DMSO- d_6) δ ppm 1.08 (t, $J=6.95$ Hz, 3 H) 1.19 (t, $J=7.07$ Hz, 3 H) 3.37 - 3.43 (m, 2 H)
 3.81 (q, $J=7.24$ Hz, 2 H) 4.15 (s, 2 H) 5.09 (s, 2 H) 5.22 (s, 1 H).

62b) 2-({5-Chloro-2-[(1-ethyl-3-[(ethyloxy)methyl]-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide

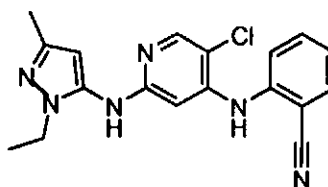


The title compound was prepared substantially as described in Example 59 except using 1-ethyl-3-[(ethyloxy)methyl]-1H-pyrazol-5-amine instead of 5-amino-1-methyl-1H-pyrazole. LCMS (M+H)⁺ = 429.1 (M+H); ¹H NMR (400 MHz, MeOD) δ ppm 1.21 (t, J=7.07 Hz, 3 H) 1.34 (t, J=7.33 Hz, 3 H) 2.91 (s, 3 H) 3.55 (q, J=6.91 Hz, 2 H) 4.04 (q, J=7.33 Hz, 2 H) 4.43 (s, 2 H) 6.22 (s, 1 H) 6.66 (s, 1 H) 7.10 - 7.20 (m, 1 H) 7.45 - 7.53 (m, 1 H) 7.53 - 7.58 (m, 1 H) 7.66 (dd, J=7.83, 1.52 Hz, 1 H) 7.93 (s, 1 H).

Example 63

2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-hydroxy-N-methylbenzamide

63a) 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzonitrile

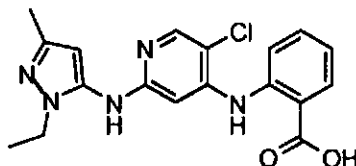


To a 50 mL tube was added 2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (738 mg, 2.80 mmol), 1-ethyl-3-methyl-1H-pyrazol-5-amine (350 mg, 2.80 mmol), BINAP (696 mg, 1.118 mmol), cesium carbonate (2733 mg, 8.39 mmol) and palladium(II) acetate (62.8 mg, 0.280 mmol) in 1,4-dioxane (15 mL). The reaction mixture was heated to 120° C for 18 hr. Solid was filtered off and discarded and the solution was concentrated. Product was then dissolved in 1 M HCl (1 mL) and extracted with EtOAc. The organic layer was discarded. The water layer was neutralized with 1 M NaOH (to pH 8) and extracted with EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄, filtered and evaporated. The solid was dissolved in 20 mL of EtOAc and 20 mL of water and 1 mL of acetic acid were added. The organic layer was separated, washed with brine, dried over MgSO₄, filtered and evaporated. 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-

pyrazol-5-yl)amino]-4-pyridinyl}amino)benzonitrile (450 mg, 1.275 mmol, 45.6 % yield) was isolated as orange foam. This product was used in the next step without further purification.

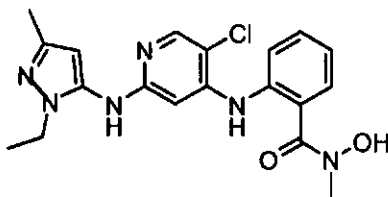
LCMS (M+H)⁺ = 353.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 (t, *J*=7.20 Hz, 3 H) 1.91 (s, 3 H) 3.84 (q, *J*=7.24 Hz, 2 H) 5.92 (s, 1 H) 6.03 (s, 1 H) 7.41 (td, *J*=7.64, 0.88 Hz, 1 H) 7.48 (d, *J*=8.08 Hz, 1 H) 7.76 (td, *J*=7.83, 1.52 Hz, 1 H) 7.91 (dd, *J*=7.83, 1.52 Hz, 1 H) 7.96 (s, 1 H) 8.47 (d, *J*=7.07 Hz, 1 H) 11.98 (br. s., 1 H)

63b) 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid



To a 50 mL round bottom flask was added 2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzonitrile (300 mg, 0.850 mmol), and NaOH 1 M solution (10 ml, 10.00 mmol) in 1,4-dioxane (10 mL). The mixture was heated under reflux for 18 hours. Ethyl acetate was added (20 mL) and the layers separated - all product stayed in the water phase. The water phase was neutralized with 6 N HCl, and 40 mL of ethyl acetate were added. The organic layer was separated, washed with brine, dried over MgSO₄, filtered and evaporated. 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid (220 mg, 0.562 mmol, 66.1 % yield) was isolated as off-white solid and used in the next step without further purification. LCMS (M+H)⁺ = 372.1; ¹H NMR (400 MHz, MeOD) δ ppm 1.33 (t, *J*=7.20 Hz, 4 H) 2.22 (s, 3 H) 4.00 (q, *J*=7.33 Hz, 2 H) 6.01 (s, 1 H) 6.82 (s, 1 H) 7.06 (td, *J*=7.52, 1.14 Hz, 1 H) 7.39 - 7.49 (m, 1 H) 7.49 - 7.55 (m, 1 H) 7.87 - 7.94 (m, 1 H) 8.05 (dd, *J*=7.83, 1.52 Hz, 1 H).

63c) 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-hydroxy-N-methylbenzamide



A solution of 2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid (55 mg, 0.148 mmol), HOBT (22.65 mg, 0.148 mmol) and EDC (28.4 mg, 0.148 mmol) in N,N-dimethylformamide (DMF) (5 mL) was stirred under nitrogen at room temp for 30 minutes. To this solution was added N-methylhydroxylamine (12.35 mg, 0.148 mmol) and the solution was stirred for another 15 minutes. The reaction mixture was cooled to 5°

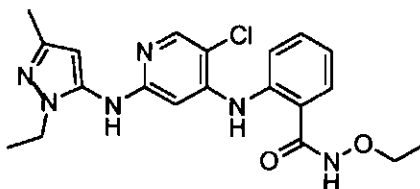
45

C and DIEA (0.052 mL, 0.296 mmol) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified using preparative HPLC (0.1% formic acid, 5 to 95% water:acetonitrile). Fractions were combined and evaporated. 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-hydroxy-N-methylbenzamide (16 mg, 0.034 mmol, 23.05 % yield) isolated as a white solid. LCMS (M+H)⁺ = 401.0 (M+H); ¹H NMR (400 MHz, MeOD) δ ppm 1.30 (t, J=7.20 Hz, 3 H) 2.19 (s, 3 H) 3.37 (d, J=1.52 Hz, 3 H) 3.96 (q, J=7.07 Hz, 2 H) 5.95 (s, 1 H) 6.32 (s, 1 H) 7.21 - 7.33 (m, 1 H) 7.42 - 7.53 (m, 2 H) 7.56 (d, J=7.33 Hz, 1 H) 7.86 (s, 1 H).

10

Example 64

2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(ethyloxy)benzamide

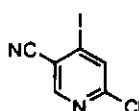


The title compound was prepared substantially as described in Example 63 except using O-ethylhydroxylamine hydrochloride instead of N-methylhydroxylamine. LCMS (M+H)⁺ = 415.1(M+H); ¹H NMR (400 MHz, MeOD) δ ppm 1.23 - 1.42 (m, 6 H) 2.21 (s, 3 H) 3.87 - 4.10 (m, 4 H) 5.99 (s, 1 H) 6.59 (s, 1 H) 7.11 - 7.28 (m, 1 H) 7.46 - 7.71 (m, 3 H) 7.92 (s, 1 H).

20

Intermediate 13

6-Chloro-4-iodo-nicotinonitrile

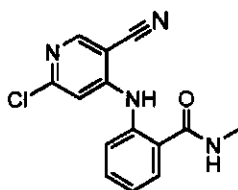


To a mixture of THF (100 mL) and hexane (40 mL) under nitrogen atmosphere was added DIPA (22.21 mL, 158.78 mmole, 1.1 eq). The mixture was cooled to -80°C and to this was added n-BuLi (63.57 mL, 158.78 mmole, 1.1 eq) dropwise. After completion of addition the resulting mixture was allowed to warm and stirred at -10°C for 15 min. The reaction mixture was again cooled to -80°C and a solution of 6-chloro-nicotinonitrile (20 g, 144.35 mmol, 1 eq) in THF (100 mL) was added dropwise. The resulting mixture was stirred at -80°C for 1h. After 1h a solution of iodine (43.96 g, 173.22 mmole, 1.2 eq) in THF (100 mL) was added in one portion. After completion of the reaction, the reaction was quenched with water (100 mL) and extracted with diethyl ether (6×100 mL). Combined organic layers were washed with saturated solution of

sodium thiosulfate (2×100 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give crude product. Crude compound was purified by column chromatography over silica gel (100-200 mesh) using 2% ethyl acetate-hexane as the eluant to yield the title compound as a faintly yellow solid (15 g, 39%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.38 (s, 1H), 8.79 (s, 1H). LC-MS calculated for C₆H₂ClIN₂ (M+H) 264.90, found 264.9.

Intermediate 14

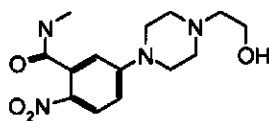
2-(2-Chloro-5-cyanopyridin-4-ylamino)-N-methylbenzamide



A mixture of 6-chloro-4-iodo-nicotinonitrile (14 g, 53.03 mmole, 1 eq), 2-amino-*N*-methoxy-benzamide (7.96 g, 53.03 mmole, 1 eq) and K₃PO₄ (28.14 g, 132.57 mmole, 2.5 eq) in 1,4-dioxane (250 mL) was degassed with N₂ for 1 h. To this mixture were added Pd(OAc)₂ (0.238 g, 1.06 mmole, 0.02 eq) and DPEPhos (2.28 g, 4.24 mmole, 0.08 eq). The resulting reaction mixture was degassed with N₂ for another 15 min after which the resulting reaction mixture was stirred at 110°C overnight. After completion of reaction solid material was collected by filtration, dissolved in water (500 mL), and extracted with ethyl acetate (5×200 mL). Combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude material. It was purified by column chromatography over silica gel (60-120 mesh) using 0.2% methanolic ammonia (10% ammonia in MeOH) in dichloromethane as the eluant to give the title compound as a pale yellow solid (9 g, 59%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 2.75 (d, 3H, *J* = 4.56 Hz), 7.09 (s, 1H), 7.25-7.35 (m, 1H), 7.53-7.60 (m, 2H), 7.72 (d, 1H, *J* = 7.48 Hz), 8.56 (s, 1H), 8.69-8.79 (brs, 1H), 10.65 (s, 1H). LC-MS calculated for C₁₄H₁₁ClN₄O (M+H) 287.06, found 286.9.

Intermediate 15

5-[4-(2-Hydroxyethyl)-1-piperazinyl]-N-methyl-2-nitrobenzamide 3

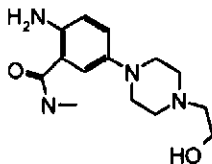


A solution of 5-fluoro-*N*-methyl-2-nitrobenzamide, 1-(2-hydroxyethyl)piperazine, and Hunig's base in 20 mL of DMF was stirred at room temperature over the weekend. The resulting

mixture was rotavaped to dryness, and the residue was purified by flash column SF40-150 at 2%-10% MeOH/CH₂Cl₂. Product came out at 7% MeOH/ CH₂Cl₂. MS(ES) m/e 309 [M+H].

Intermediate 16

5 2-amino-5-[4-(2-Hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 4

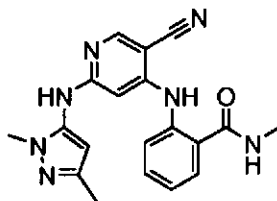


A solution of 5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methyl-2-nitrobenzamide 3 in 250 mL of MeOH in a 250 mL round bottom flask was stirred at room temperature under hydrogen balloon over night. The resulted mixture was filtered to get rid of the Pd catalyst. TLC in 10% MeOH/CH₂Cl₂ showed no more starting material and a major product. The solvent was rotavaped to dryness, and the residue was used without further purification. MS(ES) m/e 279 [M+H].

10

Example 65

2-({5-Cyano-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide



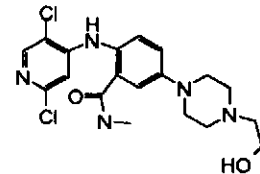
15

2-({5-Cyano-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide was synthesized substantially according to the procedure of example 55 using Intermediate 15 and 5-amino-1,3-dimethylpyrazole. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 2.08 (d, 3H), 2.77 (d, 3H), 3.53 (s, 3H), 6.01 (s, 1H), 6.59 (s, 1H), 6.01 (s, 1H), 7.18 (t, 1H), 7.54 (t, 2H), 7.72 (d, 1H), 8.33 (s, 1H), 8.71 (d, 1H), 9.15 (s, 1H), 10.33 (s, 1H). LC-MS (M+H)⁺ = 362.0.

20

Example 66

2-[(2,5-Dichloro-4-pyridinyl)amino]-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 6



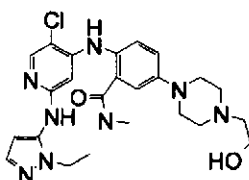
25

A sealed tube was charged with 2,5-dichloro-4-iodopyridine, 2-amino-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 4, and cesium carbonate in 1,4-dioxane. The reaction mixture was degassed by nitrogen for 10 min. At same time BINAP and palladium(II) acetate were added into it and the reaction mixture was heated in 120° C in an oil bath over night.

- 5 TLC in 10% EtOAc/hexane showed no 2,5-dichloro-4-iodopyridine. TLC in 10% MeOH/CH₂Cl₂ showed no 2-amino-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide. LCMS showed the reaction had a peak that could be the desired product. While the reaction mixture temperature was maintained at around 80° C, it was filtered, and the solid was washed with THF and CH₃CN. The solid was filtered, dried by vacuum, and purified by flash column 1-
10 8% MeOH/CH₂Cl₂, to give the captioned product as a brown oil. MS(ES) m/e 426 [M+2H].

Example 67

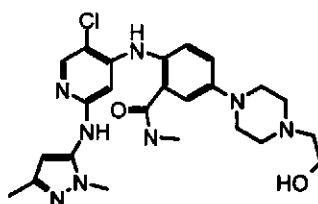
2-((5-Chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino)-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 9



- 15 A sealed tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 6, 1-ethyl-1H-pyrazol-5-amine, and cesium carbonate in 1,4-dioxane. The reaction mixture was degassed by nitrogen for 10 min. At same time, BINAP and palladium(II) acetate were added and the reaction mixture was heated to 160 °C
20 in microwave for 40 minutes. LCMS showed a peak believed to be the desired product. The solvent was rotavaped to dryness, and the residue was purified by HPLC to give the captioned product. MS(ES) m/e 500 [M+H].

Example 68

- 25 2-((5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl)amino)-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 10

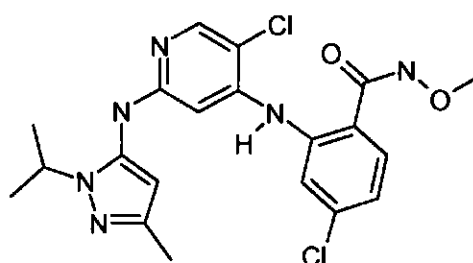


- 30 A sealed tube was charged with 2-[(2,5-dichloro-4-pyridinyl)amino]-5-[4-(2-hydroxyethyl)-1-piperazinyl]-N-methylbenzamide 6, 1-ethyl-1H-pyrazol-5-amine, and cesium

carbonate in 1,4-dioxane. The reaction mixture was degassed by nitrogen for 10 min. Then BINAP and palladium(II) acetate were added into it, and the reaction mixture was heated to 160° C in microwave for 40 minutes. LCMS showed the a peak believed to correspond to the desired product. The solvent was rotavaped to dryness, and the residue was purified by HPLC to give product. MS(ES) m/e 500 [M+H].

Example 69

4-Chloro-2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-N-(methoxy)benzamide



Step 1:

To a degassed solution of 2,5-dichloro-4-iodopyridine (4.5 g, 16.43 mmol), 2-amino-4-chlorobenzonitrile (2.507 g, 16.43 mmol) and potassium triphosphate (10.46 g, 49.3 mmol) in 1,4-dioxane (60 ml) stirred under nitrogen at the room temperature was added DPEPhos (0.708 g, 1.314 mmol) and palladium acetate (0.148 g, 0.657 mmol). The reaction mixture was stirred at the reflux for 18 hr. The reaction mixture was filtered. The solution was evaporated. Ether (50ml) was added and the formed solid was filtered. 4-chloro-2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (2.8 g, 9.38 mmol, 57.1 % yield) was isolated as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.70 (s, 1 H) 7.53 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.65 (d, *J*=2.02 Hz, 1 H) 7.95 (d, *J*=8.34 Hz, 1 H) 8.28 (s, 1 H) 9.12 (br. s., 1 H); HPLC *R*_t= 3.50 min, MS (ESI): 298.0, 300.0 [M+H]⁺.

Step 2.

A solution of 4-chloro-2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (2.8 g, 9.38 mmol), 3-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (1.305 g, 9.38 mmol) and cesium carbonate (9.17 g, 28.1 mmol) in 1,4-dioxane (40 mL) was degassed. DPEPhos (0.404 g, 0.750 mmol) followed by palladium acetate (0.084 g, 0.375 mmol) were added, and the suspension was refluxed overnight. The solid was filtered, the reaction mixture was evaporated. The black oil was purified by flush column chromatography on silica gel (5 % EtOAc:DCM). The combined fractions were evaporated. The resulting oil was dissolved in dioxane (20mL) and sodium hydroxide (20 mL,

20.00 mmol) was added and the reaction mixture was refluxed overnight. The layers were separated and the organic layer was washed with 20 ml of 1 M NaOH. The aqueous layers were combined and washed with EtOAc. The combined organic layers were washed with water, brine and dried over MgSO_4 and filtered. The solution was evaporated, suspended in acetonitrile and
5 filtered. 4-Chloro-2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]benzoic acid (260 mg, 0.619 mmol, 6.60 % yield) was isolated as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.28 (d, $J=6.57$ Hz, 6 H) 1.91 (s, 1 H) 2.13 (s, 3 H) 4.43 (quin, $J=6.57$ Hz, 1 H) 5.97 (s, 1 H) 6.78 (s, 1 H) 7.05 (dd, $J=8.46, 1.89$ Hz, 1 H) 7.48 (d, $J=1.77$ Hz, 1 H) 7.96 (d, $J=8.34$ Hz, 1 H) 8.03 (s, 1 H) 8.61 (s, 1 H); HPLC $R_t=2.70$ min, MS (ESI):
10 420.1, 422.0 $[\text{M}+\text{H}]^+$.

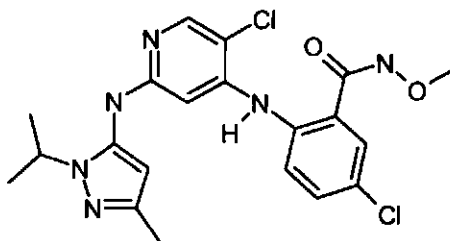
Step 3.

To the solution of 4-chloro-2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]benzoic acid (260 mg, 0.619 mmol) in N,N -dimethylformamide
15 (DMF) (20 mL) was added HOBT (114 mg, 0.742 mmol) and EDC (142 mg, 0.742 mmol) and the reaction mixture was stirred for 30 min. To this solution was added O -methoxyamine hydrochloride (62.0 mg, 0.742 mmol), and after 30 min the reaction was cooled to 0°C and DIEA (0.323 mL, 1.856 mmol) was added. The reaction mixture was stirred at the room temperature over the weekend. Water (100mL) followed by acetic acid (1 mL) were added and the reaction mixture
20 was extracted with 2 x 50 ml of ethyl acetate. The organic layer was washed with 2 x 50 ml sat KHCO_3 , brine, dried over MgSO_4 and evaporated. The resulting yellow oil was purified by flash column chromatography on silica gel using DCM:EtOAc (10 % to 100%) . 4-Chloro-2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]- N -(methoxy)benzamide (85 mg, 0.180 mmol, 29.1 % yield) was isolated as white foam. ^1H NMR
25 (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.27 (d, $J=6.57$ Hz, 6 H) 2.12 (s, 3 H) 3.70 (s, 3 H) 4.41 (quin, $J=6.57$ Hz, 1 H) 5.95 (s, 1 H) 6.66 (s, 1 H) 7.01 - 7.39 (m, 1 H) 7.55 - 7.88 (m, 2 H) 8.02 (s, 1 H) 8.60 (s, 1 H) 9.76 (br. s., 1 H) 12.01 (br. s., 1 H); HPLC $R_t=2.50$ min, MS (ESI): 449.0, 451.1 $[\text{M}+\text{H}]^+$.

48

Example 70

4-Chloro-2-[(5-chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino]-N-(methoxy)benzamide



5

Step 1:

To a degassed solution of 2,5-dichloro-4-iodopyridine (4.5 g, 16.43 mmol), 2-amino-5-chlorobenzonitrile (2.507 g, 16.43 mmol) and potassium triphosphate (10.46 g, 49.3 mmol) in 1,4-dioxane (60 ml) stirred under nitrogen at the room temperature was added DPEPhos (0.708 g, 1.314 mmol) and palladium acetate (0.148 g, 0.657 mmol). The reaction mixture was stirred at reflux for 18 hr. The reaction mixture was filtered. The reaction mixture was evaporated. Ether (50ml) was added and the solid was filtered. 5-chloro-2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (1.8 g, 5.43 mmol, 33.0 % yield) was isolated as orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.63 (s, 1 H) 7.52 (d, *J*=8.59 Hz, 1 H) 7.81 (dd, *J*=8.59, 2.53 Hz, 1 H) 8.09 (d, *J*=2.53 Hz, 1 H) 8.24 (s, 1 H) 9.06 (br. s., 1 H); HPLC Rt= 3.53 min, MS (ESI): 298.0, 299.9 [M+H]⁺.

Step 2.

To a solution of 5-chloro-2-[(2,5-dichloro-4-pyridinyl)amino]benzonitrile (1.8 g, 6.03 mmol) and 3-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (0.839 g, 6.03 mmol) in 1,4-dioxane (40 mL) was added cesium carbonate (5.89 g, 18.09 mmol) and the reaction mixture was degassed. DPEPhos (0.260 g, 0.482 mmol) was added followed by palladium acetate (0.054 g, 0.241 mmol) and the reaction mixture was heated to reflux overnight. The suspension was then filtered. The dioxane was evaporated. Solid was partitioned between 1 M HCl and ethyl acetate. Layers were separated, and organic layer discarded. The HCl-containing layer was neutralized and extracted with 2 x 50 mL of ethyl acetate. Organic layers were combined, washed with brine, dried over MgSO₄, filtered and evaporated. 5-Chloro-2-[(5-chloro-2-[(3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino)-4-pyridinyl]amino]benzonitrile (850 mg, 2.118 mmol, 35.1 % yield) was isolated as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.25 (d, *J*=6.57 Hz, 6 H) 2.09 (s, 3 H) 4.35 (quin, *J*=6.57 Hz, 1 H) 5.89 (s, 1 H) 6.03 (s, 1 H) 7.46 (d, *J*=8.84 Hz, 1 H) 7.81 (dd,

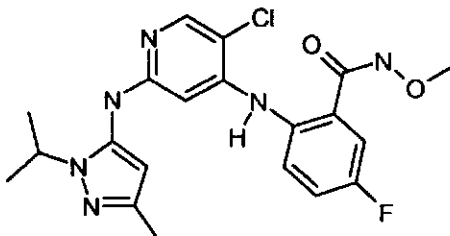
$J=8.72, 2.65$ Hz, 1 H) 7.96 (s, 1 H) 8.11 (d, $J=2.53$ Hz, 1 H) 8.42 (s, 1 H) 8.54 (s, 1 H) HPLC Rt= 2.60 min, MS (ESI): 400.8, 403.1 $[M+H]^+$.

Step 3.

- 5 A solution of 5-chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzonitrile (850 mg, 2.118 mmol) in sodium hydroxide - 1 M (20 mL, 20.00 mmol) and 1,4-dioxane (20 mL) was refluxed overnight. Ethyl acetate was added and the layers were separated. The organic layer was washed with 1 M NaOH (40 ml). Combined aqueous layers were washed with ethyl acetate. The organic layers were combined, evaporated, 10 dissolved in MeOH and evaporated again. 5-Chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzoic acid (800 mg, 1.903 mmol, 90 % yield) was isolated as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.28 (d, $J=6.57$ Hz, 6 H) 2.12 (s, 3 H) 4.40 (quin, $J=6.51$ Hz, 1 H) 5.97 (s, 1 H) 6.79 (s, 1 H) 7.56 - 7.62 (m, 1 H) 7.62 - 7.69 (m, 1 H) 7.94 (d, $J=2.27$ Hz, 1 H) 8.04 (s, 1 H) 8.58 (s, 1 H) 9.94 (br. s., 1 H) 13.97 (br. s., 1 H); HPLC 15 Rt= 2.65 min, MS (ESI): 420.2, 421.1 $[M+H]^+$.

Step 4.

- To a solution of 5-chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]benzoic acid (830 mg, 1.975 mmol) in N,N-dimethylformamide (20 mL) was added HOBT (363 mg, 2.370 mmol) and EDC (454 mg, 2.370 mmol) and the reaction 20 mixture was stirred for 30 min. To this solution was added o-methoxyamine hydrochloride (198 mg, 2.370 mmol) and after 30 min the mixture was cooled to 0° C. DIEA (1.032 mL, 5.92 mmol) was added. The reaction mixture was stirred at the room temperature over the weekend. Water (100mL) was added followed by acetic acid (1 mL) and the solution extracted with 2 x 50 ml of 25 ethyl acetate. The organic layer was washed with 2 x 50 ml sat KHCO_3 , brine, dried over MgSO_4 and evaporated. The product was purified by flash column chromatography on silica gel using EtOAc:DCM (10 % to 100%). 5-Chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-N-(methoxy)benzamide (250 mg, 0.529 mmol, 26.8 % yield) was isolated as a white foam. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.27 (d, $J=6.57$ Hz, 6 H) 30 2.11 (s, 3 H) 3.71 (s, 3 H) 4.20 - 4.55 (m, 1 H) 5.94 (s, 1 H) 6.63 (s, 1 H) 7.59 (s, 2 H) 7.67 (s, 1 H) 7.99 (s, 1 H) 8.50 (s, 1 H) 9.43 (br. s., 1 H) 12.03 (br. s., 1 H); HPLC Rt= 2.46 min, MS (ESI): 449.1, 451.1 $[M+H]^+$.

Example 712-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluoro-N-(methoxy)benzamide

5

Step 1:

To a degassed solution of 2,5-dichloro-4-iodopyridine (8 g, 29.2 mmol), 2-amino-5-fluorobenzonitrile (3.98 g, 29.2 mmol) and potassium triphosphate (18.60 g, 88 mmol) in 1,4-dioxane (100 ml) stirred under nitrogen at the room temperature was added DPEPhos (1.258 g, 2.337 mmol) and palladium acetate (0.262 g, 1.168 mmol). The reaction mixture was stirred at the reflux for 18 hr. The reaction mixture was filtered. The solvent was evaporated. Ether (50ml) was added and the solid was filtered. 2-[(2,5-Dichloro-4-pyridinyl)amino]-5-fluorobenzonitrile (7.09 g, 25.1 mmol, 86 % yield) was isolated as an orange solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 6.44 (s, 1 H) 7.46 - 7.58 (m, 2 H) 7.66 (dd, *J*=8.08, 2.78 Hz, 1 H) 8.08 (s, 1 H); HPLC Rt= 3.23 min, MS (ESI): 382.0, 384.19 [M+H]⁺.

Step 2.

To a solution of 2-[(2,5-dichloro-4-pyridinyl)amino]-5-fluorobenzonitrile (7.09 g, 25.1 mmol) and 3-methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (3.5 g, 25.1 mmol) in 1,4-dioxane (100 mL) was added cesium carbonate (24.58 g, 75 mmol) and the reaction mixture was degassed. DPEPhos (1.083 g, 2.012 mmol) was added followed by palladium acetate (0.226 g, 1.006 mmol) and the reaction mixture was heated to reflux overnight. The suspension was then filtered. The dioxane was evaporated off. The solid was purified by flash column chromatography on silica gel (10 % DCM: EtOAC). Fractions were collected and evaporated. The yellow oil was dissolved in diethyl ether, sonicated and filtered. 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluorobenzonitrile (1.3 g, 3.21 mmol, 12.76 % yield) was isolated as a white solid; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.35 (d, *J*=6.82 Hz, 6 H) 2.20 (s, 3 H) 4.43 (quin, *J*=6.69 Hz, 1 H) 5.82 (s, 1 H) 5.89 (s, 1 H) 7.47 - 7.57 (m, 2 H) 7.61 - 7.74 (m, 1 H) 7.88 (s, 1 H); HPLC Rt= 2.40 min, MS (ESI): 385.2 [M+H]⁺.

Step 3.

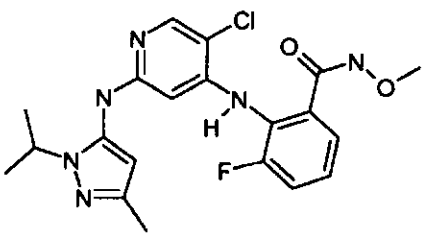
A solution of 2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluorobenzonitrile (1.3 g, 3.38 mmol) in sodium hydroxide - 1 M (10 mL, 10.00 mmol) and 1,4-dioxane (10 mL) was refluxed overnight. Ethyl acetate was added and the layers were separated. The organic layer was washed with 1 M NaOH (40 mL). The combined aqueous layers were washed with ethyl acetate, and neutralized with acetic acid. The product was isolated by filtration. 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluorobenzoic acid (1.1 g, 2.72 mmol, 27.2 % yield) was isolated as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (d, *J*=6.57 Hz, 6 H) 2.11 (s, 3 H) 4.39 (quin, *J*=6.57 Hz, 1 H) 5.95 (s, 1 H) 6.70 (s, 1 H) 7.51 (td, *J*=8.40, 3.16 Hz, 1 H) 7.61 (dd, *J*=9.09, 4.80 Hz, 1 H) 7.72 (dd, *J*=9.22, 3.16 Hz, 1 H) 8.00 (s, 1 H) 8.53 (s, 1 H) 9.66 (br. s., 1 H) 13.88 (br. s., 1 H); HPLC Rt= 2.44 min, MS (ESI): 404.3 [M+H]⁺.

Step 4.

To the solution of 2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluorobenzoic acid (1128 mg, 2.79 mmol) in N,N-dimethylformamide (DMF) (20 mL) was added HOBt (513 mg, 3.35 mmol) followed by EDC (643 mg, 3.35 mmol) and the reaction mixture stirred for 30 min. To this solution was added o-methoxyamine hydrochloride (280 mg, 3.35 mmol) and after 30 min, at 0°C DIEA (1.460 mL, 8.38 mmol) was added. The reaction mixture was stirred at room temperature 24 hr. Water (100 mL) was added followed by acetic acid (1 mL) and the solution extracted with 2 x 50 mL of ethyl acetate. The organic layer was separated, washed with 2 x 50 mL sat KHCO₃, brine, dried over MgSO₄ and evaporated. The resulting oil was suspended in dichloromethane and filtered. 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluoro-N-(methoxy)benzamide (620 mg, 1.361 mmol, 48.7 % yield) was isolated as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.26 (d, *J*=6.57 Hz, 6 H) 2.10 (s, 3 H) 3.69 (s, 3 H) 4.38 (quin, *J*=6.57 Hz, 1 H) 5.92 (s, 1 H) 6.50 (s, 1 H) 7.41 - 7.52 (m, 2 H) 7.58 (dd, *J*=8.72, 4.67 Hz, 1 H) 7.96 (s, 1 H) 8.46 (s, 1 H) 9.10 (s, 1 H) 11.95 (s, 1 H); HPLC Rt= 2.24 min, MS (ESI): 433.4 [M+H]⁺.

Example 72

2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-3-fluoro-N-(methoxy)benzamide



5

Step 1:

To a degassed solution of 2,5-dichloro-4-iodopyridine (8 g, 29.2 mmol), 2-amino-3-fluorobenzonitrile (3.98 g, 29.2 mmol) and potassium triphosphate (18.60 g, 88 mmol) in 1,4-dioxane (60 ml) stirred under nitrogen at the room temperature was added DPEPhos (1.258 g, 2.337 mmol) and palladium acetate (0.262 g, 1.168 mmol). The reaction mixture was stirred at reflux for 18 hr. The reaction mixture was filtered. 3-Methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (4.07 g, 29.2 mmol) and cesium carbonate (28.6 g, 88 mmol) were added. The reaction mixture was degassed and palladium acetate (0.262 g, 1.168 mmol) and DPEPhos (1.258 g, 2.337 mmol) were added. The reaction mixture was refluxed overnight. The reaction mixture was filtered and the solid was dissolved in water, heated to 50° C and stirred for 10 minutes, then filtered again. 2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-3-fluorobenzonitrile (6 g, 15.59 mmol, 53.4 % yield) was isolated as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 (d, *J*=6.57 Hz, 6 H) 2.07 (s, 3 H) 4.32 (quin, *J*=6.57 Hz, 1 H) 5.64 (d, *J*=2.02 Hz, 1 H) 5.83 (s, 1 H) 7.39 - 7.58 (m, 1 H) 7.63 - 7.82 (m, 2 H) 7.88 (s, 1 H) 8.26 (br. s., 1 H) 8.41 (br. s., 1 H); HPLC *R*_t= 2.35 min, MS (ESI): 385.0 [M+H]⁺.

Step 2.

A solution of 2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-3-fluorobenzonitrile (4.5 g, 11.69 mmol) in sodium hydroxide - 1 M (10 mL, 10.00 mmol) and 1,4-dioxane (10 mL) was refluxed overnight. Ethyl acetate was added and the layers were separated. The organic layer was washed with 1 M NaOH (40 ml). Combined aqueous layers were washed with ethyl acetate, and neutralized with acetic acid. The solid was filtered. 2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-3-fluorobenzoic acid (3.2 g, 7.53 mmol, 75 % yield) was isolated as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.24 (d, *J*=6.57 Hz, 6 H) 2.09 (s, 3 H) 4.34 (quin, *J*=6.57 Hz, 1 H) 5.86 (s, 1 H) 5.91 (d, *J*=5.81 Hz, 1 H) 7.35 (td, *J*=8.02, 4.93 Hz, 1 H) 7.54 - 7.65 (m, 1 H) 7.81 (d, *J*=7.58

Hz, 1 H) 7.94 (s, 1 H) 8.45 (s, 1 H) 8.88 (br. s., 1 H) 13.74 (br. s., 1 H); HPLC Rt= 2.36 min, MS (ESI): 404.3 [M+H]⁺.

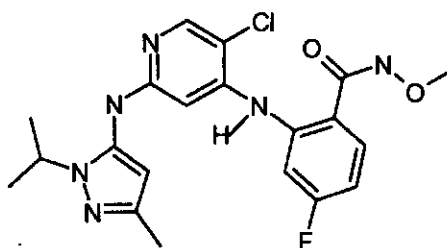
Step 3.

5 To a solution of 2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-3-fluorobenzoic acid (3.2 g, 7.92 mmol) in N,N-dimethylformamide (DMF) (50 mL) was added HOBT (1.456 g, 9.51 mmol) and EDC (1.823 g, 9.51 mmol) and the reaction mixture was stirred for 30 min. To this solution was added O-methoxylamine hydrochloride (0.794 g, 9.51 mmol). After 30 min the reaction mixture was cooled to 0° C and DIEA (4.14 mL, 23.77 mmol) was added. The reaction mixture was stirred at the room temperature 24 hr. Water (100mL) was added followed by acetic acid (1 mL) and the solution was extracted with 2 x 50 ml of ethyl acetate. The combined organic layers were washed with 2 x 50 ml sat KHCO₃, brine, dried over MgSO₄ and evaporated. The oil was suspended in dichloromethane and filtered. 2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-3-fluoro-N-(methoxy)benzamide (1.1 g, 2.414 mmol, 30.5 % yield) was isolated as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.24 (d, *J*=6.57 Hz, 6 H) 2.08 (s, 3 H) 3.68 (s, 3 H) 4.33 (quin, *J*=6.57 Hz, 1 H) 5.83 (d, *J*=5.05 Hz, 1 H) 5.84 (s, 1 H) 7.30 - 7.49 (m, 2 H) 7.49 - 7.63 (m, 1 H) 7.92 (s, 1 H) 8.41 (d, *J*=4.29 Hz, 2 H) 11.85 (s, 1 H); HPLC Rt= 2.18 min, MS (ESI): 433.3 [M+H]⁺.

20

Example 73

2-[(5-Chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-4-fluoro-N-(methoxy)benzamide



25

Step 1:

To a degassed solution of 2,5-dichloro-4-iodopyridine (5 g, 18.26 mmol), 2-amino-4-fluorobenzonitrile (2.485 g, 18.26 mmol) and potassium triphosphate (11.63 g, 54.8 mmol) in 1,4-dioxane (60 ml) stirred under nitrogen at the room temperature was added DPEPhos (0.787 g, 1.460 mmol) and palladium acetate (0.164 g, 0.730 mmol). The reaction mixture was stirred at the

reflux for 18 hr. The reaction mixture was filtered. 3-Methyl-1-(1-methylethyl)-1H-pyrazol-5-amine (2.54 g, 18.26 mmol) and cesium carbonate (17.84 g, 54.8 mmol) were added. The reaction mixture was degassed and palladium acetate (0.164 g, 0.730 mmol) and DPEPhos (0.787 g, 1.460 mmol) were added. The reaction mixture was refluxed overnight. The reaction mixture was
5 filtered. NaOH (60 mL, 60.0 mmol) was added and the reaction mixture refluxed overnight. Ethyl acetate was added and the layers were separated. The combined organics were washed with 1 M NaOH (40 mL). The combined aqueous layers were washed with ethyl acetate, and neutralized with acetic acid. 2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-4-fluorobenzoic acid (2.5 g, 6.19 mmol, 33.9 % yield) was isolated by filtration
10 as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (d, *J*=6.57 Hz, 6 H) 2.12 (s, 3 H) 4.43 (quin, *J*=6.57 Hz, 1 H) 5.99 (s, 1 H) 6.86 (s, 1 H) 6.87 - 6.93 (m, 1 H) 7.34 (dd, *J*=11.62, 2.53 Hz, 1 H) 8.03 - 8.10 (m, 2 H) 8.62 (s, 1 H) 10.65 (br. s., 1 H); HPLC Rt= 2.57 min, MS (ESI): 404.2 [M+H]⁺.

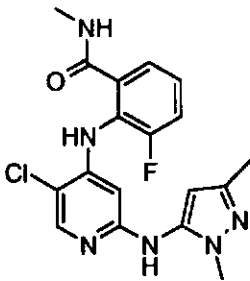
15 Step 2.

To a solution of 2-[(5-chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-4-fluorobenzoic acid (2.5 g, 6.19 mmol) in N,N-dimethylformamide (DMF) (50 mL) was added HOBT (1.138 g, 7.43 mmol) and EDC (1.424 g, 7.43 mmol) and the reaction mixture was stirred for 30 min. To this solution was added O-methoxyamine hydrochloride (0.620
20 g, 7.43 mmol) and after 30 min the mixture was cooled to 0° C. Then DIEA (3.23 mL, 18.57 mmol) was added. The reaction mixture was stirred at the room temperature for 24 hr. Water (100 mL) followed by acetic acid (1 mL) were added and the solution extracted with 2 x 50 mL of ethyl acetate. The organic layer was washed with 2 x 50 mL sat KHCO₃, brine, dried over MgSO₄ and condensed. The resulting oil was purified by flash column chromatography on silica gel (2: 1
25 DCM: EtOAc). 2-[(5-Chloro-2-[[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino]-4-pyridinyl)amino]-4-fluoro-N-(methoxy)benzamide (1 g, 2.195 mmol, 35.5 % yield) was isolated as a yellow foam. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.28 (d, *J*=6.57 Hz, 6 H) 2.11 (s, 3 H) 3.71 (s, 3 H) 4.41 (quin, *J*=6.51 Hz, 1 H) 5.97 (s, 1 H) 6.74 (s, 1 H) 6.87 - 7.06 (m, 1 H) 7.39 (dd, *J*=11.37, 2.53 Hz, 1 H) 7.66 (dd, *J*=8.46, 6.69 Hz, 1 H) 8.03 (s, 1 H) 8.57 (s, 1 H) 9.96 (br. s., 1 H)
30 11.98 (br. s., 1 H); HPLC Rt= 2.36 min, MS (ESI): 433.3 [M+H]⁺.

Example 74

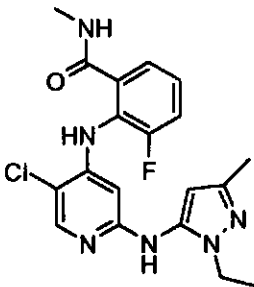
Following substantially the procedure of Example 8 the following compounds can be made starting with either 2,5-dichloro-4-iodopyridine or 2-chloro-4-iodo-5-(trifluoromethyl)pyridine and the appropriately substituted 5-aminopyrazole.
35

74(a). 2-({5-Chloro-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

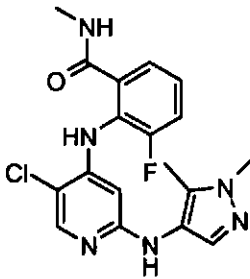


5

74(b). 2-({5-Chloro-2-[(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

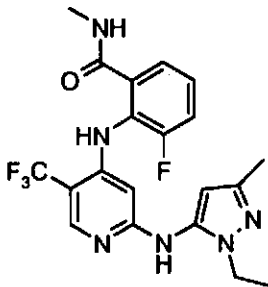


74(c). 2-({5-Chloro-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide



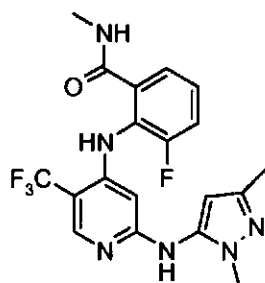
10

74(d). 2-({2-[(1-Ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

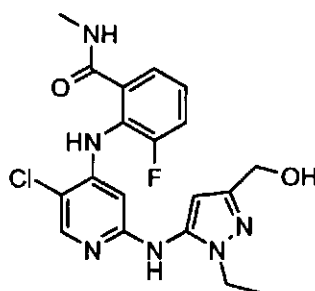


52

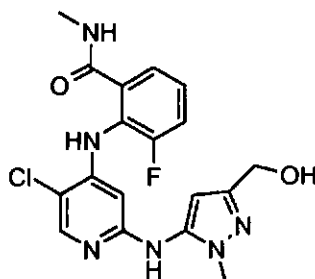
74(e). 2-{{2-[(1,3-Dimethyl-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino}-3-fluoro-*N*-methylbenzamide



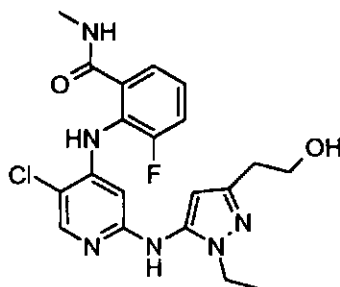
74(f). 2-{{2-[[1-Ethyl-3-(hydroxymethyl)-1*H*-pyrazol-5-yl]amino]-5-chloro-4-pyridinyl}amino}-3-fluoro-*N*-methylbenzamide



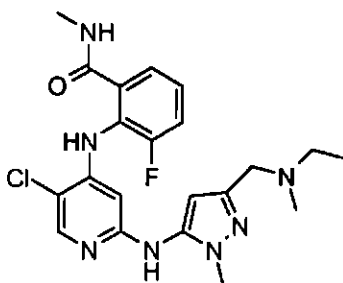
74(g). 3-Fluoro-2-{{2-[[3-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl]amino]-5-chloro-4-pyridinyl}amino}-*N*-methylbenzamide



74(h). 2-{{2-[[1-Ethyl-3-(2-hydroxyethyl)-1*H*-pyrazol-5-yl]amino]-5-chloro-4-pyridinyl}amino}-3-fluoro-*N*-methylbenzamide

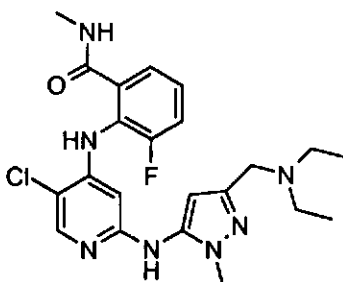


74(l). 2-({5-Chloro-2-[(3-{[ethyl(methyl)amino]methyl}-1-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

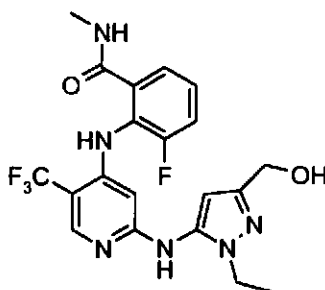


5

74(m). 2-({5-chloro-2-[(3-{[diethylamino]methyl}-1-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

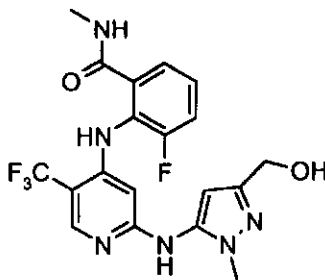


74(n). 2-({2-[(1-Ethyl-3-(hydroxymethyl)-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-3-fluoro-*N*-methylbenzamide

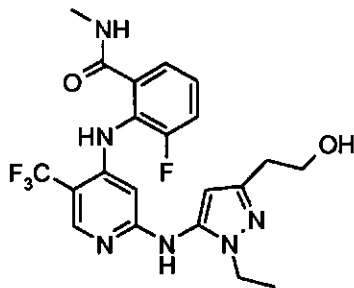


10

74(o). 3-Fluoro-2-({2-[(3-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-*N*-methylbenzamide

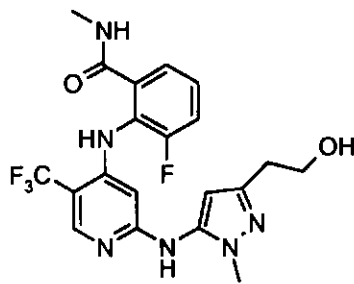


74(p). 2-{{2-{{1-Ethyl-3-(2-hydroxyethyl)-1*H*-pyrazol-5-yl}amino}-5-(trifluoromethyl)-4-pyridinyl}amino}-3-fluoro-*N*-methylbenzamide

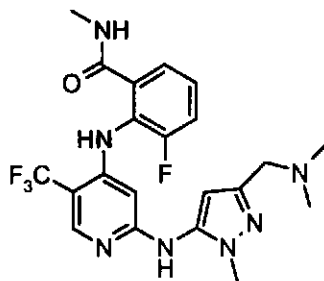


5

74(q). 3-Fluoro-2-{{2-{{3-(2-hydroxyethyl)-1-methyl-1*H*-pyrazol-5-yl}amino}-5-(trifluoromethyl)-4-pyridinyl}amino}-*N*-methylbenzamide



74(r). 2-{{2-{{3-((Dimethylamino)methyl)-1-methyl-1*H*-pyrazol-5-yl}amino)-5-(trifluoromethyl)-4-pyridinyl}amino}-3-fluoro-*N*-methylbenzamide



10

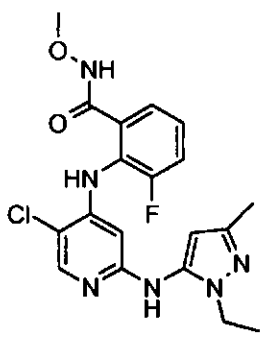
Example 75

Following substantially the procedure of Example 72 the following compounds can be made using the appropriately substituted 5-aminopyrazole.

15

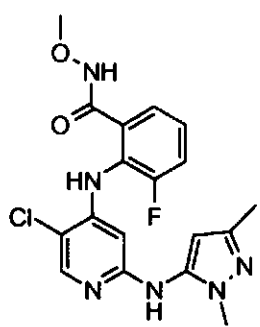
59

75(a). 2-((5-Chloro-2-((1-ethyl-3-methyl-1H-pyrazol-5-yl)amino)-4-pyridinyl)amino)-3-fluoro-N-(methoxy)benzamide

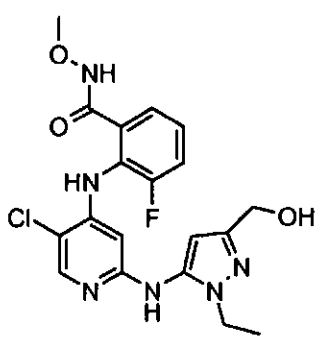


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75(b). 2-((5-Chloro-2-((1,3-dimethyl-1H-pyrazol-5-yl)amino)-4-pyridinyl)amino)-3-fluoro-N-(methoxy)benzamide

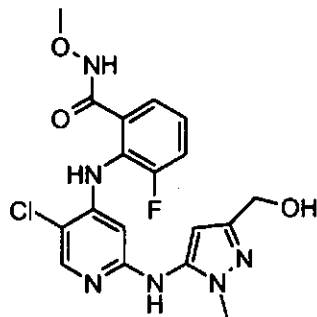


75(c). 2-((5-Chloro-2-((1-ethyl-3-(hydroxymethyl)-1H-pyrazol-5-yl)amino)-4-pyridinyl)amino)-3-fluoro-N-(methoxy)benzamide

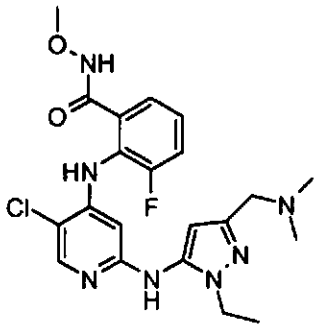


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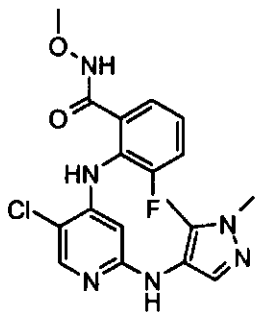
75(d). 2-[(5-Chloro-2-([3-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl]amino)-4-pyridinyl]amino]-3-fluoro-*N*-(methyloxy)benzamide



5 75(e). 2-[[5-Chloro-2-([3-[(dimethylamino)methyl]-1-ethyl-1*H*-pyrazol-5-yl]amino)-4-pyridinyl]amino]-3-fluoro-*N*-(methyloxy)benzamide



75(f). 2-[(5-Chloro-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl]amino]-3-fluoro-*N*-(methyloxy)benzamide

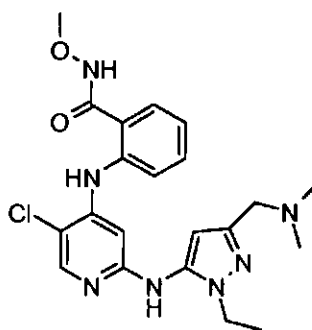


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Example 76

Following substantially the procedure of Example 41a or 41b the following compound can be made using 3-[(dimethylamino)methyl]-1-ethyl-1*H*-pyrazol-5-amine.

2-({5-Chloro-2-({3-[(dimethylamino)methyl]-1-ethyl-1H-pyrazol-5-yl}amino)-4-pyridinyl}amino)-N-(methyloxy)benzamide



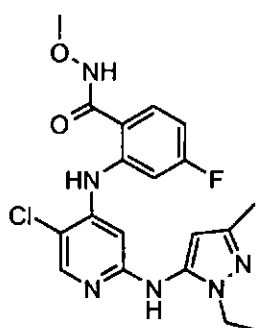
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Example 77

Following substantially the procedure of Example 73 the following compounds can be made using the appropriately substituted 5-aminopyrazole.

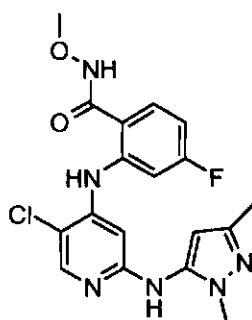
77(a). 2-({5-Chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-4-fluoro-N-(methyloxy)benzamide

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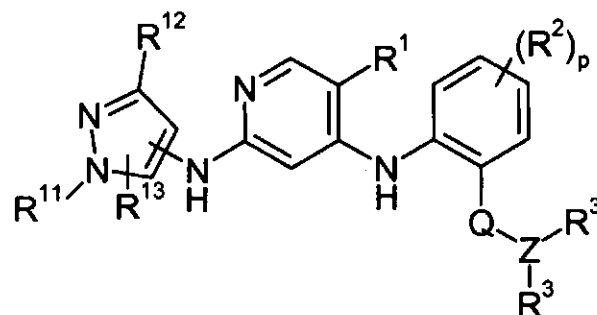
77(b). 2-({5-Chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-4-fluoro-N-(methyloxy)benzamide

15



What is claimed is:

1. A compound of formula (I):



(I)

or a salt thereof, wherein:

R¹ is halo, CF₃, C₁-C₆-alkyl, isopropenyl, (C₂-C₆-alkylene) C₃-C₆-cycloalkyl, C₁-C₆-alkoxy, or cyano;

in R², when p is other than 0, each R² is independently F, Cl, CF₃, methyl, methoxy, CH₂CF₃, -(X)_q-C₁-C₄-alkylene-R⁴, -(X-C₁-C₄-alkylene)_q-NR⁵-C(O)-R⁶, -(X-C₁-C₄-alkylene)_q-(NR⁵)_q-SO_x-R⁷, -(X-C₁-C₄-alkylene)_q-Y-N(R⁸)₂, a 5- to 6-membered heterocycloalkyl-(R⁹)_q group, or a 5- to 6-membered heteroaryl-(R¹⁰)_r group;

R³ is H, C₃-C₆-cycloalkyl, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylene-R⁴, O-C₁-C₆-alkylene-R⁴, or, the R³ groups, together with Z, form a 5- to 6-membered cyclic ring optionally substituted with methyl, C₁-C₄-alkylene-R⁴, or C₃-C₆-cycloalkyl;

R⁴ is H, -(Q)_q-N(R⁸)₂, OH, SH, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, or a 5- to 6-membered heterocycloalkyl-(R⁹)_q group;

R⁵ is H or C₁-C₆-alkyl;

R⁶ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, N(R⁸)₂, or a 5- to 6-membered heteroaryl-(R¹⁰)_r group;

R⁷ is C₁-C₆-alkyl, phenyl-(R⁹)_q, or 5- to 6-membered heteroaryl-(R¹⁰)_r;

R⁸ is independently H, C₁-C₆-alkyl, -O-C₁-C₆-alkyl or, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group;

R⁹ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, -(Q)_q-N(R⁸)₂, -Q-C₁-C₆-alkyl, -C₁-C₆-alkyl-R⁴, or 5- to 6-membered heterocycloalkyl;

R¹⁰ is H, C₁-C₆-alkyl, C₁-C₆-alkoxy, or -Q-C₂-C₆-alkyl;

R^{11} is C_1 - C_6 -alkyl, CF_3 , $-CH_2CF_3$, $-(Q)_q-C_1-C_4$ -alkylene- R^4 , $-Q-N(R^8)_2$, phenyl- $(R^5)_s$, a 5- to 6-membered heterocycloalkyl- $(R^9)_q$ group, or a 5- to 6-membered heteroaryl- $(R^{10})_r$ group;

R^{12} is H, C_1 - C_6 -alkyl, F, Cl, CF_3 , OH, CN, nitro, COOH, $-COO-C_1-C_6$ -alkyl, $-Y-N(R^8)_2$, C_3 - C_6 -cycloalkyl- R^{14} , $-(X)_q-C_1-C_6$ -alkylene- R^4 , $-(X-C_1-C_6$ -alkylene) $_q$ - $NR^5-C(O)-R^6$, $-(X-C_1-C_6$ -alkylene) $_q$ -(NR^5) $_q$ - SO_x-R^7 , $-(X-C_1-C_6$ -alkylene) $_q$ - $Y-N(R^8)_2$, heterocycloalkyl- $(R^9)_q$, heteroaryl- $(R^{10})_r$, or phenyl- $(R^{15})_s$;

R^{13} is H, F, Cl, C_1 - C_6 -alkyl, or C_3 - C_6 -cycloalkyl; or R^{12} and R^{13} , together with the carbon atoms to which they are attached, form a fused 5- or 6-membered carbocycloalkyl or heterocycloalkyl group;

R^{14} is independently H, C_1 - C_6 -alkyl, $-NR^5-SO_2-R^7$, $-Y-N(R^8)_2$, or $-(X)_q-C_1-C_6$ -alkylene- R^4 ;

each R^{15} is independently F, Cl, CF_3 , C_1 - C_3 -alkyl, or C_1 - C_3 -alkoxy;

p is 0, 1, 2, or 3;

q is 0 or 1;

r is 0, 1, or 2;

s is 0, 1, 2, or 3;

x is 1 or 2;

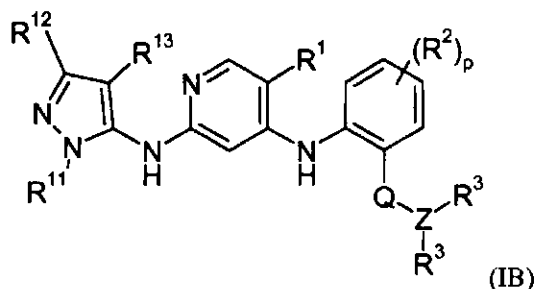
Q is $-C(O)-$, $-S(O)-$, or $-SO_2-$;

X is NR^5 , O, S, $-S(O)-$, or $-SO_2-$;

Y is a bond, SO_2 , or $C(O)$; and

Z is N or CR^5 .

2. A compound according to claim 1 which is represented by formula (IB):



or a salt thereof.

3. A compound according to claim 1 or 2 or a salt thereof wherein Q is $C(O)$ and Z is N.

4. The compound of any of claims 1 to 3 or a salt thereof where one R³ is methoxy and the other R³ is H.
5. The compound of any of claims 1 to 3 or a salt thereof where one R³ is methyl and the other R³ is H.
6. A compound according to any of claims 1 to 5 or a salt thereof wherein R¹ is Cl, CF₃, or CN.
7. A compound according to any one of claims 1 to 6 or a salt thereof wherein p is 0 or 1 and R² is F.
8. A compound according to any one of claims 1 to 7 or a salt thereof wherein R¹¹ is C₁-C₃-alkyl.
9. The compound of any of Claims 1 to 8 or a salt thereof wherein R¹² is C₁-C₄-alkyl, hydroxymethyl, or cyclopropyl.
10. A compound according to any one of Claims 1 to 9 or a salt thereof wherein R¹³ is H.
11. A compound according to claim 1 which is:
 - 2-[5-chloro-2-(2-methyl-5-phenyl-2H-pyrazol-3-ylamino)-pyridin-4-ylamino]-N-methylbenzamide;
 - 2-({5-chloro-2-[(1-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;
 - 2-({5-chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;
 - 2-[(5-chloro-2-{{3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl}amino}-4-pyridinyl)amino]-N-methylbenzamide;
 - 2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;
 - 2-({5-chloro-2-[(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;
 - 2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-4,5-difluoro-N-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-4,5-difluoro-N-methylbenzamide;

5-chloro-2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;

5-chloro-2-({5-chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;

2-[(5-chloro-2-({3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl}amino)-4-pyridinyl)amino]-N-methylbenzamide;

2-[(5-chloro-2-({1-ethyl-3-(hydroxymethyl)-1H-pyrazol-5-yl}amino)-4-pyridinyl)amino]-N-methylbenzamide;

2-[(5-chloro-2-({1-(2-hydroxyethyl)-3-methyl-1H-pyrazol-5-yl}amino)-4-pyridinyl)amino]-N-methylbenzamide;

ethyl 5-({5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-1-ethyl-1H-pyrazole-3-carboxylate;

5-({5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-1-ethyl-1H-pyrazole-3-carboxylic acid;

5-({5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-1-ethyl-N-(methoxy)-1H-pyrazole-3-carboxamide;

5-({5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-1-ethyl-N-methyl-1H-pyrazole-3-carboxamide;

2-[(5-chloro-2-({3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl}amino)-4-pyridinyl)amino]-N-methylbenzamide;

2-[(5-chloro-2-({1-(1-methyl-4-piperidinyl)-1H-pyrazol-5-yl}amino)-4-pyridinyl)amino]-N-methylbenzamide;

2-({5-chloro-2-({1-[2-(dimethylamino)ethyl]-3-methyl-1H-pyrazol-5-yl}amino)-4-pyridinyl}amino)-N-methylbenzamide;

5-{{5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-N-[2-(dimethylamino)ethyl]-1-ethyl-1H-pyrazole-3-carboxamide;

5-{{5-chloro-4-({2-[(methylamino)carbonyl]phenyl}amino)-2-pyridinyl}amino)-N-[2-(dimethylamino)ethyl]-1-ethyl-N-methyl-1H-pyrazole-3-carboxamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino)-N-methylbenzamide;

2-{{2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-N-methylbenzamide;

2-{{2-[(1-ethyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-N-methylbenzamide;

N-methyl-2-{{2-{{3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl}amino}-5-(trifluoromethyl)-4-pyridinyl}amino}benzamide;

2-{{2-{{1-[2-(dimethylamino)ethyl]-3-methyl-1H-pyrazol-5-yl}amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-N-methylbenzamide;

2-{{2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-N-methylbenzamide;

N-methyl-2-{{2-{{3-methyl-1-phenyl-1H-pyrazol-5-yl}amino]-5-(trifluoromethyl)-4-pyridinyl}amino}benzamide;

2-{{2-{{1-(2-hydroxyethyl)-3-methyl-1H-pyrazol-5-yl}amino]-5-(trifluoromethyl)-4-pyridinyl}amino)-N-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)benzoic acid;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-methyl-N-(methyloxy)benzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-{{2-(dimethylamino)ethyl}oxy}benzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide;

2-({5-chloro-2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-N-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide HCl;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide formate;

2-({5-chloro-2-[(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-ethylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-ethylbenzamide;

2-({5-chloro-2-[(1-ethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-ethylbenzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-ethylbenzamide;

2-({5-chloro-2-({1-ethyl-3-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazol-5-yl}amino)-4-pyridinyl}amino)-*N*-methylbenzamide;

2-({5-chloro-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl}amino)-*N*-(methyloxy)benzamide;

2-({5-chloro-2-[(1,3-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl}amino)-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[4-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

2-({5-chloro-2-[(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[4-methyl-1-(2-methylpropyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-(hydroxymethyl)-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

2-[5-cyclopropyl-2-(2,5-dimethyl-2*H*-pyrazol-3-ylamino)-pyridin-4-ylamino]-*N*-methylbenzamide;

2-[5-cyclopropyl-2-(2-ethyl-5-methyl-2*H*-pyrazol-3-ylamino)-pyridin-4-ylamino]-*N*-methylbenzamide;

2-[5-cyclopropyl-2-(2,5-dimethyl-2*H*-pyrazol-3-ylamino)-pyridin-4-ylamino]-*N*-methoxybenzamide;

2-[5-cyclopropyl-2-(2-ethyl-5-methyl-2*H*-pyrazol-3-ylamino)-pyridin-4-ylamino]-*N*-methoxybenzamide;

2-[2-(2,5-dimethyl-2*H*-pyrazol-3-ylamino)-5-isopropenyl-pyridin-4-ylamino]-*N*-methylbenzamide;

2-[2-(2,5-dimethyl-2*H*-pyrazol-3-ylamino)-5-isopropyl-pyridin-4-ylamino]-*N*-methylbenzamide;

2-({5-chloro-2-[(1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl}amino)-*N*-methylbenzamide;

2-{[5-chloro-2-({1-ethyl-3-[(methyloxy)methyl]-1*H*-pyrazol-5-yl}amino)-4-pyridinyl]amino}-*N*-methylbenzamide;

2-{[5-chloro-2-({1-ethyl-3-[(methyloxy)methyl]-1*H*-pyrazol-5-yl}amino)-4-pyridinyl]amino}-*N*-methylbenzamide;

2-[(5-chloro-2-{[3-[(ethyloxy)methyl]-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-methylbenzamide;

2-[(5-chloro-2-{[3-[(ethyloxy)methyl]-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-methylbenzamide;

2-{[5-chloro-2-({1-ethyl-3-[(ethyloxy)methyl]-1*H*-pyrazol-5-yl}amino)-4-pyridinyl]amino}-*N*-methylbenzamide;

2-{[5-chloro-2-({1-ethyl-3-[(ethyloxy)methyl]-1*H*-pyrazol-5-yl}amino)-4-pyridinyl]amino}-*N*-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-hydroxy-*N*-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-hydroxy-*N*-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-(ethyloxy)benzamide;

2-({5-cyano-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-*N*-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-[4-(2-hydroxyethyl)-1-piperazinyl]-*N*-methylbenzamide;

2-({5-chloro-2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl}amino)-5-[4-(2-hydroxyethyl)-1-piperazinyl]-*N*-methylbenzamide;

4-chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

4-chloro-2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1*H*-pyrazol-5-yl]amino}-4-pyridinyl)amino]-5-fluoro-*N*-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-3-fluoro-N-(methyloxy)benzamide;

2-[(5-chloro-2-{[3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]amino}-4-pyridinyl)amino]-4-fluoro-N-(methyloxy)benzamide;

2-({5-chloro-2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-[(1,5-dimethyl-1H-pyrazol-4-yl)amino]-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-{[2-[(1-ethyl-3-methyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

2-{[2-[(1,3-dimethyl-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

2-{[2-[(1-ethyl-3-(hydroxymethyl)-1H-pyrazol-5-yl)amino]-5-chloro-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

3-fluoro-2-{[2-{[3-(hydroxymethyl)-1-methyl-1H-pyrazol-5-yl]amino}-5-chloro-4-pyridinyl]amino}-N-methylbenzamide;

2-{[2-[(1-ethyl-3-(2-hydroxyethyl)-1H-pyrazol-5-yl)amino]-5-chloro-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

3-fluoro-2-{[2-{[3-(2-hydroxyethyl)-1-methyl-1H-pyrazol-5-yl]amino}-5-chloro-4-pyridinyl]amino}-N-methylbenzamide;

2-{[2-({3-[(dimethylamino)methyl]-1-methyl-1H-pyrazol-5-yl}amino)-5-chloro-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

2-{[2-({3-[(dimethylamino)methyl]-1-ethyl-1H-pyrazol-5-yl}amino)-5-chloro-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-({3-([ethyl(methyl)amino)methyl]-1-methyl-1H-pyrazol-5-yl}amino)-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-({5-chloro-2-({3-[(diethylamino)methyl]-1-methyl-1H-pyrazol-5-yl}amino)-4-pyridinyl}amino)-3-fluoro-N-methylbenzamide;

2-{[2-[(1-ethyl-3-(hydroxymethyl)-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

3-fluoro-2-{[2-{[3-(hydroxymethyl)-1-methyl-1H-pyrazol-5-yl]amino}-5-(trifluoromethyl)-4-pyridinyl]amino}-N-methylbenzamide;

2-{[2-[(1-ethyl-3-(2-hydroxyethyl)-1H-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino}-3-fluoro-N-methylbenzamide;

3-fluoro-2-([2-([3-(2-hydroxyethyl)-1-methyl-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino)-*N*-methylbenzamide;

2-([2-([3-([dimethylamino)methyl]-1-methyl-1*H*-pyrazol-5-yl)amino]-5-(trifluoromethyl)-4-pyridinyl]amino)-3-fluoro-*N*-methylbenzamide;

2-([5-chloro-2-([1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1-ethyl-3-(hydroxymethyl)-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([3-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([3-([dimethylamino)methyl]-1-ethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl]amino)-3-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([3-([dimethylamino)methyl]-1-ethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1-ethyl-3-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1-ethyl-3-(hydroxymethyl)-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1-ethyl-3-(2-hydroxyethyl)-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([3-(hydroxymethyl)-1-methyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([3-([dimethylamino)methyl]-1-ethyl-1*H*-pyrazol-5-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide;

2-([5-chloro-2-([1,5-dimethyl-1*H*-pyrazol-4-yl)amino]-4-pyridinyl]amino)-4-fluoro-*N*-(methyloxy)benzamide; or

a salt or a thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/62163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/535 (2010.01)

USPC - 514/236.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/236.5 (see search terms below)Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/341; 546/275.4; 546/272.1; 544/124 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: amine derivatives, treatment, cancer, angiogenesis, tyrosine kinases, VEGFR, inhibitory activity, Fak, pyridyl, pyrazolyl, carboxamide, VEGFR2, crystal structure, catalytic site, binding site, drug design, 3-dimensional models. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/007481 A2 (PATEL et al.) 22 January 2004 (22.01.2004), pg 6, ln 1 - pg 20, ln 4; pg 84, ln 20-27; pg 76, ln 24 - pg 77, ln 17; pg 85, ln 5-8.	1-3 and 11
Y	WO 00/14105 A1 (MCTIGUE et al.) 16 March 2000 (16.03.2000), pg 1, ln 5-15; pg 6, ln 25-27; pg 7, ln 28-30; pg 17, ln 10 - pg 24, ln 30; Fig 1-4; Fig 7.	1-3 and 11

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

15 January 2010 (15.01.2010)

Date of mailing of the international search report

13 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/62163

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10 and 12-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

PIRAZOLILAMINOPIRIDINAS COMO INHIBIDORES DE FAK

ÁREA DE LA INVENCION

Esta invención se refiere a una clase de pirazolilaminopiridinas que inhiben la quinasa de adhesión focal (FAK), así como composiciones de las mismas. Los compuestos de la presente invención son útiles en el tratamiento de enfermedades proliferativas incluyendo, pero sin limitación, cánceres.

ANTECEDENTES DE LA INVENCION

Las tirosina quinasas desempeñan un papel importante en la regulación de muchos procesos celulares, incluyendo proliferación celular, supervivencia celular y migración celular. Se sabe que ciertas tirosina quinasas se activan por mutación o se expresan de forma normal en muchos cánceres humanos. Por ejemplo, el receptor del factor de crecimiento epidérmico (EGFR) se encuentra mutado y/o sobreexpresado en cánceres de mama, pulmón, cerebro, células escamosas, gástrico y otros cánceres humanos. Se ha demostrado que los inhibidores selectivos de la actividad tirosina quinasa de EGFR son de valor clínico en el tratamiento de cánceres con EGFR mutado y/o sobreexpresado. Por lo tanto, los inhibidores selectivos de tirosina quinasas particulares son útiles en el tratamiento de enfermedades proliferativas tales como cánceres.

La FAK (codificada por el gen PTK2) es una tirosina quinasa no receptora que integra señales de integrinas y receptores de factores de crecimiento. Se ha descrito que la FAK desempeña un papel en la regulación de supervivencia, crecimiento, adhesión, migración e invasión celular (McLean et al 2005, Nat Rev Cancer 5: 505-515). Además, la FAK se regula y activa por fosforilación en múltiples restos de tirosina. La sobreexpresión de ARNm y/o proteína FAK se ha documentado en muchos tumores sólidos humanos incluyendo, pero sin limitación, cánceres de mama, colon, glándula tiroides, pulmón, ovario y próstata; pero también se incluyen cánceres de origen hematológico incluyendo, pero sin limitación, leucemia tal como leucemia mieloide aguda (AML). (Owens et al. 1995, Cancer Research 55: 2752-2755; Agochiya et al. 1999, Oncogene 18: 5646-5653; Gabarro-Niecko et al. 2003, Cancer Metastasis Rev. 22: 359-374; Recher et al. 2004, Cancer Research 64: 3191-3197, Zhao y Guan, 28:35-49, 2009, Cancer Metastasis Rev.). Más significativamente, existen pruebas de que la FAK fosforilada está aumentada en tejidos tumorales en comparación con tejidos normales (Grisaru-Granovsky et al. 2005, int. J. Cancer 113: 372-378) y podría representar un

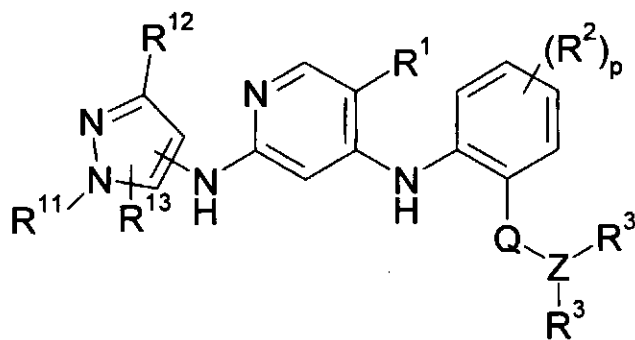
marcador de pronóstico de metástasis. La actividad de la FAK está claramente implicada en el cáncer humano avanzado y metastásico (Zhao y Guan, 28: 35-49, 2009, Cancer Metastasis Rev.).

Se ha demostrado que la eliminación de la FAK por ARNi o la expresión de una FAK dominante negativa induce una pérdida de adhesión y muerte celular en líneas celulares de mama y melanoma humanas, y aumenta la apoptosis mediada por docetaxel en células de cáncer de ovario (Beviglia et al 2003, Biochem J. 373: 201-210, Smith et al 2005, Melanoma Res. 15: 357-362, Halder et al 2005, Clin. Cancer Res. 11: 8829-8836). Sin embargo, se descubrió que la inhibición de la FAK en fibroblastos humanos normales o en células mamarias inmortalizadas (MCF10A) no causaba pérdida de unión o apoptosis (Xu et al. 1996 Cell Growth and Diff 7: 413-418). También se ha demostrado que la inhibición de la FAK por expresión dominante negativa reduce el desarrollo tumoral y elimina la metástasis pulmonar de células de adenocarcinoma mamario en un modelo singénico de rata (van Nimwegen et al 2005, Cancer Res. 65: 4698-4706). De forma similar, la inhibición de la FAK por ARNsh inhibía la metástasis pulmonar y reducía la letalidad en 40% en un modelo singénico de ratón (Mitra et al 2006, Oncogene 25: 4429-4440). En este estudio, la re-expresión transitoria de tipo silvestre, pero no de FAK sin actividad quinasa, revertía los fenotipos ARNsh. La inhibición de la FAK por expresión dominante negativa en células de carcinoma 4T1 de ratón reducía el desarrollo tumoral y la angiogénesis en ratones (Mitra et al 2006, Oncogene 25: 5969-5984). Además, la pérdida de actividad catalítica de FAK (reconstitución de células FAK -/- con FAK sin actividad quinasa) reducía el desarrollo de tumores v-Src en ratones y disminuía la angiogénesis.

Por lo tanto, existen pruebas firmes que sugieren que la inhibición de la actividad de la FAK induce apoptosis, pérdida de adhesión, inhibición del desarrollo y de la migración celular, y que dicha inhibición reduce la angiogénesis. Por consiguiente, los compuestos que inhiben la actividad de la FAK serían útiles para el tratamiento de cánceres.

COMPENDIO DE LA INVENCION

La presente invención se refiere a compuestos de fórmula (I):



(I)

o a una sal de los mismos, donde:

R¹ es halo, CF₃, alquilo C₁-C₆, isopropenilo, (alquilenos C₂-C₆)-cicloalquilo C₃-C₆, alcoxi C₁-C₆ o ciano;

en R², cuando p es distinto de 0, cada R² es independientemente F, Cl, CF₃, metilo, metoxi, CH₂CF₃, -(X)_q-alquilenos C₁-C₄-R⁴, -(X-alquilenos C₁-C₄)_q-NR⁵-C(O)-R⁶, -(X-alquilenos C₁-C₄)_q-(NR⁵)_q-SO_x-R⁷, -(X-alquilenos C₁-C₄)_q-Y-N(R⁸)₂; un grupo heterocicloalquil de 5 a 6 miembros-(R⁹)_q o un grupo heteroaril de 5 a 6 miembros-(R¹⁰)_r;

R³ es independientemente H, cicloalquilo C₃-C₆, alquilo C₁-C₆, alcoxi C₁-C₆, alquilenos C₁-C₆-R⁴, O-alquilenos C₁-C₆-R⁴, o, los grupos R³, junto con Z, forman un anillo cíclico de 5 a 6 miembros opcionalmente sustituido con metilo, alquilenos C₁-C₄-R⁴ o cicloalquilo C₃-C₆;

R⁴ es H, -(Q)_q-N(R⁸)₂, OH, SH, alcoxi C₁-C₆, tioalquilo C₁-C₆ o un grupo heterocicloalquil de 5 a 6 miembros-(R⁹)_q;

R⁵ es H o alquilo C₁-C₆;

R⁶ es H, alquilo C₁-C₆, alcoxi C₁-C₆, N(R⁸)₂ o un grupo heteroaril de 5 a 6 miembros-(R¹⁰)_r;

R⁷ es alquilo C₁-C₆, fenil-(R⁹)_q o heteroaril de 5 a 6 miembros-(R¹⁰)_r;

R⁸ es independientemente H, alquilo C₁-C₆, -O-alquilo C₁-C₆ o, junto con el átomo de nitrógeno al que están unidos, forman un grupo heterocicloalquilo de 5 ó 6 miembros;

R⁹ es H, alquilo C₁-C₆, alcoxi C₁-C₆, -(Q)_q-N(R⁸)₂, -Q-alquilo C₁-C₆, -alquil C₁-C₆-R⁴ o heterocicloalquilo de 5 a 6 miembros;

R¹⁰ es H, alquilo C₁-C₆, alcoxi C₁-C₆ o -Q-alquilo C₂-C₆;

R¹¹ es alquilo C₁-C₆, CF₃, -CH₂CF₃, -(Q)_q-alquilenos C₁-C₄-R⁴, -Q-N(R⁸)₂, fenil-(R⁵)_s, un grupo heterocicloalquil de 5 a 6 miembros-(R⁹)_q o un grupo heteroaril de 5 a 6 miembros-(R¹⁰)_r;

R^{12} es H, alquilo C_1-C_6 , F, Cl, CF_3 , OH, CN, nitro, COOH, -COO-alquilo C_1-C_6 , $-Y-N(R^8)_2$, cicloalquil $C_3-C_6-R^{14}$, $-(X)_q$ -alquilenos $C_1-C_6-R^4$, $-(X$ -alquilenos $C_1-C_6)_q$ - $NR^5-C(O)-R^6$, $-(X$ -alquilenos $C_1-C_6)_q$ - $(NR^5)_q-SO_x-R^7$, $-(X$ -alquilenos $C_1-C_6)_q$ - $Y-N(R^8)_2$, heterocicloalquil- $(R^9)_q$, heteroaril- $(R^{10})_r$ o fenil- $(R^{15})_s$;

5 R^{13} es H, F, Cl, alquilo C_1-C_6 o cicloalquilo C_3-C_6 ; o R^{12} y R^{13} , junto con los átomos de carbono a los que están unidos, forman un grupo carbocicloalquilo o heterocicloalquilo condensado de 5 ó 6 miembros;

R^{14} es independientemente H, alquilo C_1-C_6 , $-NR^5-SO_2-R^7$, $-Y-N(R^8)_2$ o $-(X)_q$ -alquilenos $C_1-C_6-R^4$;

10 R^{15} es independientemente F, Cl, CF_3 , alquilo C_1-C_3 o alcoxi C_1-C_3 ;

p es 0, 1, 2 ó 3;

q es 0 ó 1;

r es 0, 1 ó 2;

s es 0, 1, 2 ó 3;

15 x es 1 ó 2;

Q es $-C(O)-$, $-S(O)-$ o $-SO_2-$;

X es NR^5 , O, S, $-S(O)-$ o $-SO_2-$;

Y es un enlace, SO_2 o $C(O)$; y

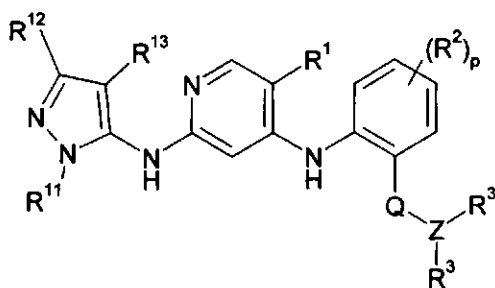
Z es N o CR^5 .

20 En una realización más, la presente invención se refiere a una composición que comprende a) el compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo; y b) un excipiente farmacéuticamente aceptable.

En una realización más, la presente invención se refiere a un método para tratar una enfermedad proliferativa tal como cáncer o una enfermedad de angiogénesis anormal tal como degeneración macular, que comprende administrar
25 a un paciente que lo necesita una cantidad farmacéuticamente eficaz del compuesto de fórmula (I).

DESCRIPCIÓN DETALLADA DE LA INVENCION

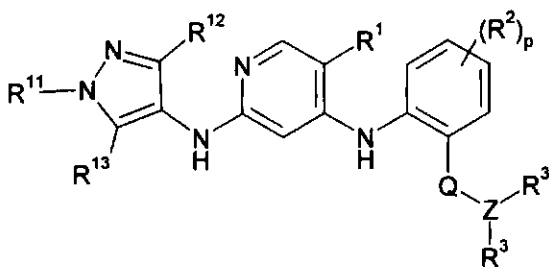
En otro aspecto, la presente invención se refiere a compuestos de fórmula
30 (Ia):



(Ia)

en la que los diversos grupos son los mismos que se han descrito anteriormente para la fórmula (I); o una sal farmacéuticamente aceptable de los mismos.

En otro aspecto, la presente invención se representa por un compuesto de fórmula (Ib):



(Ib)

en la que los diversos grupos son los mismos que se han descrito anteriormente para la fórmula (I); o una sal farmacéuticamente aceptable del mismo.

En otro aspecto de la presente invención, Q es C(O) y Z es N.

En otro aspecto de la presente invención, R¹ es Cl, CF₃ o CN;

En otro aspecto de la presente invención, R² es F;

En otro aspecto de la presente invención, un R³ es metilo y el otro R³ es H;

En otro aspecto de la presente invención, un R³ es metoxi y el otro R³ es H;

En otro aspecto de la presente invención, R¹¹ es alquilo C₁-C₆;

En otro aspecto de la presente invención, R¹² es alquilo C₁-C₆, hidroximetilo o ciclopropilo;

En otro aspecto de la presente invención, R¹³ es H;

En otro aspecto de la presente invención, p es 0 ó 1;

Como se usa en la presente memoria, "halo" se refiere a flúor, cloro o bromo.

"Alquilo C₁-C₆" se refiere a un grupo alquilo lineal o ramificado incluyendo

metilo, etilo, *n*-propilo, isopropilo, *n*-butilo, isobutilo, *t*-butilo, *n*-pentilo y *n*-hexilo.

"Alcoxi C₁-C₆" se refiere a grupos alquil C₁-C₆-O-, incluyendo grupos metoxi, etoxi, *n*-propoxi, *iso*-propoxi y *n*-butoxi.

El término "alquileo" (por ejemplo, alquileo C₂-C₄ o alquileo C₁-C₆) se refiere a un radical hidrocarburo lineal o ramificado que tiene el número especificado de átomos de carbono. El grupo "-alquileo-R⁴" se refiere a un grupo alquilo sustituido o sin sustituir que tiene el número especificado de átomos de carbono; por lo tanto, cuando R⁴ es H, "alquileo" es sinónimo de "alquilo"; por el contrario, alquileo es un radical bivalente. Los ejemplos de -(X)_q-alquileo C₂-C₄-R⁴ incluyen -CH₂CH₂-N(CH₃)₂, -CH₂CH₂-OH, -CH₂CH(CH₃)-OCH₃, -N(CH₃)-CH₂CH₂CH₂-piperidinilo; -O-CH₂CH(CH₃)-OCH₃; y similares.

Cicloalquilo C₃-C₆ se refiere a un grupo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

Como se usa en la presente memoria, "heterocicloalquilo de 5 ó 6 miembros" se refiere a un grupo cicloalifático de 5 ó 6 miembros que incluye un heteroátomo de O, N o S o una combinación de los mismos. Los ejemplos de grupos heterocicloalquilo adecuados incluyen grupos pirrolidinilo, pirrolidinonilo, piperidinilo, piperazinilo, oxopiperazinilo, morfolino y tiomorfolino.

Los grupos R⁸ pueden formar, junto con el átomo de nitrógeno al que están unidos, un anillo cíclico de 5 a 6 miembros, cuyos ejemplos incluyen grupos pirrolidinilo, pirrolidinonilo, piperidinilo, piperazinilo, oxopiperazinilo, morfolino y tiomorfolino.

El término "heteroarilo" se refiere a un grupo aromático de 5 ó 6 miembros que contiene al menos un átomo de N, O o S. Los ejemplos de grupos heteroarilo adecuados incluyen piridinilo, piridazinilo, pirimidinilo, pirazinilo, pirrolilo, furilo, tienilo, pirazolilo, imidazolilo, furazanilo, oxazolilo, tiazolilo, isoxazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo e isotiazolilo.

Como se usa en la presente memoria, "farmacéuticamente aceptable" se refiere a los compuestos, materiales, composiciones y formas de dosificación que, dentro del alcance del juicio médico, son adecuados para el uso en contacto con los tejidos de seres humanos y animales sin producir una toxicidad e irritación excesivas u otro problema o complicación.

El especialista apreciará que pueden prepararse sales farmacéuticamente aceptables de los compuestos de fórmula (I). Más particularmente, puesto que los compuestos de acuerdo con la fórmula (I) contienen un grupo funcional básico - y

pueden incluir un grupo funcional ácido - pueden formar sales farmacéuticamente aceptables por tratamiento con un ácido o base adecuada. Los ácidos adecuados incluyen ácidos inorgánicos y ácidos orgánicos farmacéuticamente aceptables. Los ácidos farmacéuticamente aceptables representativos incluyen cloruro de hidrógeno, bromuro de hidrógeno, ácido nítrico, ácido sulfúrico, ácido sulfónico, ácido fosfórico, ácido acético, ácido hidroxiaacético, ácido fenilacético, ácido propiónico, ácido butírico, ácido valérico, ácido maleico, ácido acrílico, ácido fumárico, ácido málico, ácido malónico, ácido tartárico, ácido cítrico, ácido salicílico, ácido benzoico, ácido tánico, ácido fórmico, ácido esteárico, ácido láctico, ácido ascórbico, ácido *p*-toluenosulfónico, ácido oleico y ácido láurico.

Las bases adecuadas incluyen bases inorgánicas, tales como hidruros, hidróxidos y carbonatos de litio, sodio, potasio, calcio, magnesio y cinc, así como bases orgánicas tales como arginina, colina, dietilentriamina, dimetilamina, etilendiamina, imidazol, lisina, morfina, prolina y trimetilamina.

Como se usa en la presente memoria, la expresión "un compuesto de fórmula (I)" o "el compuesto de fórmula (I)" se refiere a uno o más compuestos de acuerdo con la fórmula (I). El compuesto de fórmula (I) puede existir en una forma cristalina o no cristalina, o en forma de una mezcla de las mismas. El especialista apreciará que pueden formarse solvatos farmacéuticamente aceptables para compuestos cristalinos en los que las moléculas de disolventes se incorporan en la estructura cristalina durante la cristalización. Las moléculas de disolventes incorporadas pueden ser moléculas de agua o moléculas no acuosas tales como moléculas de etanol, isopropanol, DMSO, ácido acético, etanolamina y acetato de etilo. Las estructuras cristalina incorporadas con moléculas de agua se denominan típicamente "hidratos". Los hidratos incluyen hidratos estequiométricos así como composiciones que contienen cantidades variables de agua. La presente invención incluye todos estos solvatos.

Algunos de los compuestos descritos en la presente memoria pueden contener uno o más átomos quirales, o por el contrario pueden ser capaces de existir en forma de dos enantiómeros. Los compuestos reivindicados más adelante incluyen mezclas de enantiómeros así como enantiómeros purificados o mezclas enantioméricamente enriquecidas. También se incluyen dentro del alcance de la invención los isómeros individuales de los compuestos representados por la fórmula (I), o reivindicados más adelante, así como cualquier mezcla total o parcialmente equilibrada de los mismos. La presente invención también incluye los isómeros

individuales de los compuestos reivindicados como mezclas con isómeros de los mismos en las que uno o más centros quirales están invertidos.

Cuando hay diferentes formas isoméricas, pueden separarse o resolverse unas de otras por métodos convencionales, o cualquier isómero dado puede
5 obtenerse por métodos sintéticos convencionales o por síntesis estereoespecífica o asimétrica.

Aunque es posible que, para el uso en terapia, un compuesto e fórmula (I), así como sales, solvatos y similares, pueda administrarse en forma de una preparación pura, es decir, sin ningún vehículo adicional, la práctica más habitual es
10 presentar el ingrediente activo preparado con un vehículo o diluyente. Por consiguiente, la invención proporciona adicionalmente composiciones farmacéuticas, que incluyen un compuesto de fórmula (I) y sales, solvatos y similares, y uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables. Los compuestos de fórmula (I) y sales, solvatos, etc, son como se han
15 descrito anteriormente. El(los) vehículo(s), diluyente(s) o excipiente(s) debe(n) ser aceptable(s) en el sentido de ser compatible(s) con los otros ingredientes de la formulación y no perjudicial(es) para el receptor de el(los) mismo(s). De acuerdo con otro aspecto de la invención, también se proporciona un proceso para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de
20 la fórmula (I), o sales, solvatos, etc, con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables.

Se apreciará por los especialistas en la técnica que algunos derivados protegidos de compuestos de fórmula (I), que pueden prepararse antes de una etapa de desprotección final, pueden no poseer actividad farmacológica por sí
25 mismos, pero, en ciertas circunstancias, pueden administrarse por vía oral o parenteral y después de ello metabolizarse en el cuerpo para formar compuestos de la invención que son farmacológicamente activos. Por lo tanto, dichos derivados pueden describirse como "profármacos". Además, algunos compuestos de la invención pueden actuar como profármacos de otros compuestos de la invención.
30 Todos los derivados protegidos y profármacos de compuestos de la invención se incluyen dentro del alcance de la invención. Se apreciará además por los especialistas en la técnica que algunos restos, conocidos por los especialistas en la técnica como "pro-restos", pueden situarse sobre funcionalidades apropiadas cuando dichas funcionalidades están presentes dentro de los compuestos de la
35 invención. Los profármacos preferidos para los compuestos de la invención

incluyen: ésteres, ésteres carbonato, hemi-ésteres, ésteres fosfato, nitro ésteres, ésteres sulfato, sulfóxidos, amidas, carbamatos, compuestos azo, fosfamidas, glicósidos, éteres, acetales y cetales.

Las composiciones farmacéuticas pueden presentarse en formas de dosis unitarias que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. Dicha unidad puede contener, por ejemplo, de 0,5 mg a 3500 mg, preferiblemente de 1 mg a 700 mg, más preferiblemente de 5 mg a 100 mg de un compuesto de la fórmula (I), dependiendo de la afección que se trate, la vía de administración y la edad, peso y estado del paciente, o las composiciones farmacéuticas pueden presentarse en formas de dosis unitarias que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. Las composiciones de dosificación unitaria preferidas son las que contienen una dosis o subdosis diaria, como se ha mencionado anteriormente en la presente memoria, o una fracción apropiada de la misma, de un ingrediente activo. Además, dichas composiciones farmacéuticas pueden prepararse por cualquiera de los métodos bien conocidos en la técnica de la farmacia.

Las composiciones farmacéuticas pueden adaptarse para administración por cualquier vía apropiada, por ejemplo por la vía oral (incluyendo bucal o sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual o transdérmica), vaginal o parenteral (incluyendo subcutánea, intramuscular, intravenosa o intradérmica). Dichas composiciones pueden prepararse por cualquier método conocido en la técnica de la farmacia, por ejemplo, asociando un compuesto de fórmula (I) con el vehículo o vehículos o excipiente o excipientes.

Las composiciones farmacéuticas adaptadas para administración oral pueden presentarse como unidades separadas tales como cápsulas o comprimidos; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; o emulsiones líquidas de aceite en agua o emulsiones líquidas de agua en aceite.

Las cápsulas se obtienen preparando una mezcla en polvo, como se ha descrito anteriormente, y rellenando las cubiertas de gelatina formadas. Pueden añadirse deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilenglicol sólido a la mezcla en polvo antes de la operación de relleno. También puede añadirse un disgregante o agente solubilizante tal como agar-agar, carbonato de calcio o carbonato de sodio para mejorar la disponibilidad del medicamento cuando se ingiere la cápsula.

Además, cuando se desee o sea necesario, también pueden incorporarse en la mezcla aglutinantes, lubricantes, agentes disgregantes y agentes colorantes adecuados. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como goma arábica, tragacanto o alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras y similares. Los lubricantes usados en estas formas de dosificación incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio y similares. Los disgregantes incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantano y similares. Los comprimidos se formulan, por ejemplo, por preparación de una mezcla en polvo, granulación o precompresión, adición de un lubricante y disgregante y prensado en comprimidos. Se prepara una mezcla en polvo por mezcla del compuesto, convenientemente triturado con un diluyente o base como se ha descrito anteriormente y, opcionalmente, con un aglutinante tal como carboximetilcelulosa, un alginato, gelatina o polivinilpirrolidona, un retardante de la disolución tal como parafina, un acelerador de la reabsorción tal como una sal cuaternaria y/o un agente de absorción tal como bentonita, caolín o fosfato dicálcico. La mezcla en polvo puede granularse mediante troqueles de formación de comprimidos por medio de la adición de ácido esteárico, una sal estearato, talco o aceite mineral. La mezcla lubricada se comprime después en comprimidos. Los compuestos de la presente invención también pueden combinarse con un vehículo inerte fluido y comprimirse en comprimidos directamente sin pasar por las etapas de granulación o precompresión. Puede proporcionarse un recubrimiento protector transparente u opaco que consiste en un recubrimiento sellante de goma laca, un recubrimiento de azúcar o un material polimérico y un recubrimiento de brillo de cera. Pueden añadirse colorantes a estos recubrimientos para distinguir dosificaciones unitarias diferentes.

Pueden prepararse fluidos orales tales como soluciones, jarabes y elixires en forma de dosificación unitaria de modo que una cantidad dada contenga una cantidad predeterminada de un compuesto de fórmula (I). Pueden prepararse jarabes disolviendo el compuesto en una solución acuosa convenientemente saborizada, mientras que los elixires se preparan mediante el uso de un vehículo alcohólico no tóxico. Pueden formularse suspensiones por dispersión del compuesto en un vehículo no tóxico. También pueden añadirse solubilizantes y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de

polioxietilen sorbitol, conservantes, aditivos saporíferos tales como aceite de menta o edulcorantes naturales o sacarina u otros edulcorantes artificiales, y similares.

Cuando sea apropiado, las composiciones farmacéuticas de dosificación unitaria para administración oral pueden microencapsularse. La formulación
5 también puede prepararse para prolongar o sostener la liberación, como por ejemplo, por recubrimiento o embebimiento del material particulado en polímeros, ceras o similares.

Las formulaciones farmacéuticas adaptadas para administración parenteral incluyen soluciones para inyección estériles acuosas y no acuosas que pueden
10 contener antioxidantes, tampones, agentes bacteriostáticos y solutos que hacen que la composición sea isotónica con la sangre del destinatario deseado; y suspensiones estériles acuosas y no acuosas que puede incluir agentes de suspensión y agentes espesantes. Las composiciones farmacéuticas pueden presentarse en envases de dosis unitarias o multidosis, por ejemplo ampollas y
15 viales sellados, y pueden almacenarse en un estado secado por congelación (liofilizado) que sólo requiere la adición del vehículo líquido estéril, por ejemplo agua para inyección, inmediatamente antes del uso. Pueden prepararse soluciones y suspensiones para inyección extemporánea a partir de polvos, gránulos y comprimidos estériles.

20 Una cantidad terapéuticamente eficaz de un compuesto de la presente invención dependerá de varios factores que incluyen, por ejemplo, la edad y peso del destinatario deseado, la afección exacta que requiere el tratamiento y su gravedad, la naturaleza de la formulación y la vía de administración, y en última instancia dependerá del criterio del médico que prescriba la medicación. Sin
25 embargo, una cantidad eficaz de un compuesto de fórmula (I) para el tratamiento de un cáncer estará generalmente en el intervalo de 0,001 a 100 mg/kg de peso corporal del destinatario por día, convenientemente en el intervalo de 0,01 a 10 mg/kg de peso corporal por día. Para un adulto de 70 kg, la cantidad real por día sería convenientemente de 7 a 700 mg y esta cantidad puede administrarse en una
30 sola dosis al día o en varias (tales como dos, tres, cuatro, cinco o seis) subdosis al día de modo que la dosis diaria total sea la misma. Una cantidad eficaz de una sal o solvato, por ejemplo, puede determinarse como una proporción de la cantidad eficaz del compuesto de fórmula (I) *per se*. Se prevé que serían apropiadas dosificaciones similares para el tratamiento de las otras afecciones a las que se ha
35 hecho referencia anteriormente.

Tratamientos

Los compuestos y composiciones de la invención se usan para tratar enfermedades de proliferación celular. Las patologías que pueden tratarse por los métodos y composiciones que se proporcionan en la presente memoria incluyen, pero sin limitación, cáncer, enfermedad autoinmune, trastornos fúngicos, artritis, rechazo de injertos, enfermedad inflamatoria del intestino, proliferación inducida después de procedimientos médicos incluyendo, pero sin limitación, cirugía, angioplastia y similares. Se aprecia que, en algunos casos, las células pueden no estar en un estado de hiper- o hipoproliferación (estado anormal) y aún así requerir tratamiento. Por ejemplo, durante la curación de heridas, las células pueden estar proliferando "Normalmente", pero puede desearse un aumento de la proliferación. Por lo tanto, en una realización, la invención de este documento incluye la aplicación a células o individuos aquejados o que se verán aquejados de forma inminente con uno cualquiera de estos trastornos o estados. Estos compuestos también pueden usarse para tratar la degeneración macular asociada con la neovascularización, tal como AMD.

Las composiciones y métodos proporcionados en la presente memoria se consideran particularmente útiles para el tratamiento de cánceres incluyendo tumores tales como carcinomas de piel, mama, cerebro, cervical, carcinomas testiculares, etc. Son particularmente útiles en el tratamiento de tumores metastásicos o malignos. Más particularmente, los cánceres que pueden tratarse mediante las composiciones y métodos de la invención incluyen, pero sin limitación, tipos tumorales tales como carcinomas y sarcomas astrocíticos, de mama, cervicales, colorrectales, endometriales, esofágicos, gástricos, de cabeza y cuello, hepatocelulares, laríngeos, pulmonares, orales, de ovario, próstata y tiroides. Más específicamente, estos compuestos pueden usarse para tratar: sarcoma cardíaco (angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma), mixoma, rabdomioma, fibroma, lipomas y teratoma; pulmón: carcinoma broncogénico (de células escamosas, de células pequeñas no diferenciado, de células grandes no diferenciado, adenocarcinoma), carcinoma alveolar (bronquiolar), adenoma bronquial, sarcoma, linfoma, hamartoma condromatoso, mesotelioma; gastrointestinal: esófago (carcinoma de células escamosas, adenocarcinoma, leiomiomasarcoma, linfoma), estómago (carcinoma, linfoma, leiomiomasarcoma), páncreas (adenocarcinoma de ductal, insulinooma, glucagonoma, gastrinooma, tumores carcinoides, vipoma), intestino delgado (adenocarcinoma, linfoma, tumores

- carcinoides, sarcoma de Kaposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), intestino grueso (adenocarcinoma, adenoma tubular, adenoma vellosos, hamartoma, leiomioma); tracto genitourinario: riñón (adenocarcinoma, tumor de Wilm (nefroblastoma), linfoma, leucemia), vejiga y uretra (carcinoma de células
- 5 escamosas, carcinoma de células de transición, adenocarcinoma), próstata (adenocarcinoma, sarcoma), testículo (seminoma, teratoma, carcinoma embrionario, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma de células intersticiales, fibroma, fibroadenoma, tumores adenomatoides, lipoma); hígado: hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma,
- 10 angiosarcoma, adenoma hepatocelular, hemangioma; hueso: sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno (sarcoma de células del retículo), mieloma múltiple, cordoma tumoral de células gigantes maligno, osteocondroma (exostosis osteocartilaginosa), condroma benigno, condroblastoma, condromixofibroma,
- 15 osteoma osteoide y tumores de células gigantes; sistema nervioso: cráneo (osteoma, hemangioma, granuloma, xantoma, osteitis deformante), meninges (meningioma, meningiosarcoma, gliomatosis), cerebro (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma (pinealoma), glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, tumores congénitos),
- 20 neurofibroma de medula espinal, meningioma, glioma, sarcoma); ginecológico: útero (carcinoma endometrial), cuello del útero (carcinoma cervical, displasia cervical pretumoral), ovarios (carcinoma ovárico) (cistoadenocarcinoma seroso, cistoadenocarcinoma mucinoso, carcinoma no clasificado), tumores de células de la granulosa-teca, tumores de células de Sertoli-Leydig, disgerminoma, teratoma
- 25 maligno), vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), vagina (carcinoma de células claras, carcinoma de células escamosas, sarcoma botrioide (rabdomyosarcoma embrionario), carcinoma de trompas de Falopio; hematológico: sangre (leucemia mieloide (aguda y crónica), leucemia linfoblástica aguda, leucemia linfocítica
- 30 crónica, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplásico), enfermedad de Hodgkin, linfoma no Hodgkin (linfoma maligno); piel: melanoma maligno, carcinoma de células basales, carcinoma de células escamosas, sarcoma de Kaposi, nevus displásico o mola, lipoma, angioma, dermatofibroma, queloides, psoriasis; y glándulas suprarrenales: neuroblastoma.
- 35 Por lo tanto, la expresión "célula cancerosa", como se proporciona en la presente

memoria, incluye una célula afectada por uno cualquiera o relacionada con las afecciones identificadas anteriormente.

En comparación con derivados de 2,4-diaminopiridina relacionados descritos en otra parte, los compuestos de la presente invención contienen una función éster de ácido hidroxámico en el anillo de 4-aminofenilo en la posición 2 y un aminopirazol en la posición 2 en el anillo de piridina. La función éster de ácido hidroxámico en el anillo de fenilo en comparación con la amida correspondiente aumenta la potencia frente a la FAK del orden de 2,5 veces, particularmente *in vitro*, y mejora la selectividad por FAK con respecto a otras enzimas. El pirazol reduce la reactividad en el citocromo P450. Por lo tanto, la combinación de la construcción de éster de ácido hidroxámico en el anillo de fenilo con un aminopirazol en posición 2 en el anillo de piridina proporciona compuestos con mayor seguridad y eficacia con respecto a otros inhibidores de FAK tales como los derivados de 2,4-diaminopiridina.

Los presentes compuestos pueden combinarse con o co-administrarse con otros agentes terapéuticos, particularmente agentes que pueden aumentar la actividad o el tiempo de disposición de los compuestos. Las terapias de combinación de acuerdo con la invención comprenden la administración de al menos un compuesto de la invención y el uso de al menos otro método de tratamiento. En una realización, las terapias de combinación de acuerdo con la invención comprenden la administración de al menos un compuesto de la invención y terapia quirúrgica. En una realización, las terapias de combinación de acuerdo con la invención comprenden la administración de al menos un compuesto de la invención y radioterapia. En una realización, las terapias de combinación de acuerdo con la invención comprenden la administración de al menos un compuesto de la invención y al menos un agente de cuidados paliativos (por ejemplo, al menos un agente antiemético). En una realización, las terapias de combinación de acuerdo con la presente invención comprenden la administración de al menos un compuesto de la invención y al menos otro agente quimioterapéutico. En una realización particular, la invención comprende la administración de al menos un compuesto de la invención y al menos un agente antineoplásico. En otra realización más, la invención comprende un régimen terapéutico donde los inhibidores de FAK de esta descripción no son por sí mismos activos o significativamente activos, pero cuando se combinan con otra terapia, que puede o no ser activa como una terapia autónoma, la combinación proporciona un resultado terapéutico útil.

Mediante la expresión "co-administración" y derivados de la misma como se usa en la presente memoria, se entiende la administración simultánea o cualquier forma de administración secuencial separada de un compuesto que inhibe la FAK, como se describe en la presente memoria, y un ingrediente o ingredientes activos adicionales, que se sabe que son útiles en el tratamiento de cánceres, incluyendo quimioterapia y tratamiento de radiación. La expresión ingrediente o ingredientes activos adicionales, como se usa en la presente memoria, incluye cualquier compuesto o agente terapéutico que se sabe que o que demuestra propiedades ventajosas cuando se administra a un paciente que necesita tratamiento para un cáncer. Preferiblemente, si la administración no es simultánea, los compuestos se administran con una estrecha proximidad en el tiempo entre sí. Además, no importa si los compuestos se administran en la misma forma de dosificación, por ejemplo, un compuesto puede administrarse por vía tópica y otro compuesto puede administrarse por vía oral.

Típicamente, cualquier agente antineoplásico que tenga actividad frente a un tumor susceptible que se trate puede co-administrarse en el tratamiento de cánceres especificados en la presente invención. Pueden encontrarse ejemplos de dichos agentes en Cancer Principles and Practice of Oncology de V.T. Devita and S. Hellman (editors), 6ª edición (15 de febrero de 2001), Lippincott Williams & Wilkins Publishers. Un especialista en la técnica sería capaz de discernir las combinaciones de agentes que serían útiles basándose en las características particulares de los fármacos y el cáncer implicado. Los agentes antineoplásicos típicos útiles en la presente invención incluyen, pero sin limitación, agentes anti-microtúbulos tales como diterpenoides y alcaloides de la vinca; complejos de coordinación de platino; agentes alquilantes tales como mostazas nitrogenadas, oxazafosforinas, alquilsulfonatos, nitrosoureas y triacenos; agentes antibióticos tales como antraciclinas, actinomicinas y bleomicinas; inhibidores de la topoisomerasa II tales como epipodofilotoxinas; antimetabolitos tales como análogos de purina y pirimidina y compuestos anti-folato; inhibidores de la topoisomerasa I tales como camptotecinas; hormonas y análogos hormonales; inhibidores de la ruta de transducción de señales; inhibidores de la angiogénesis o de tirosina quinasa no asociada a receptores; agentes inmunoterapéuticos; agentes proapoptóticos e inhibidores de la señalización del ciclo celular.

Típicamente, cualquier agente quimioterapéutico que tenga actividad contra un neoplasma susceptible de tratarse puede utilizarse en combinación con los

compuestos de la invención, siempre que el agente particular sea clínicamente compatible con la terapia que emplea un compuesto de la invención. Los agentes antineoplásicos típicos útiles en la presente invención incluyen, pero sin limitación: agentes alquilantes, antimetabolitos, antibióticos antitumorales, agentes antimitóticos, inhibidores de la topoisomerasa I y II, hormonas y análogos hormonales; retinoides, inhibidores de la ruta de transducción de señales incluyendo inhibidores del crecimiento celular o de la función de factores de crecimiento, inhibidores de la angiogénesis e inhibidores de serina/treonina quinasa u otras quinasas; inhibidores de quinasa dependiente de ciclina; terapias antisentido y agentes inmunoterapéuticos incluyendo monoclonales, vacunas u otros agentes biológicos.

Los inhibidores de la ruta de transducción de señales son los inhibidores que bloquean o inhiben un proceso químico que provoca un cambio intracelular. Como se usa en la presente memoria, este cambio es la proliferación, diferenciación o supervivencia celular. Los inhibidores de la ruta de transducción de señales útiles en la presente invención incluyen, pero sin limitación, inhibidores de tirosina quinasas asociadas a receptores, tirosina quinasas no asociadas a receptores, bloqueantes del dominio SH2/SH3, serina/treonina quinasas, fosfatidil inositol-3-OH quinasas, señalización de mioinositol y oncogenes Ras. En las composiciones y métodos descritos anteriormente pueden emplearse inhibidores de la ruta de transducción de señales en combinación con los compuestos de la invención.

También pueden encontrar utilidad en la presente invención inhibidores de la angiogénesis que son inhibidores de quinasas asociadas a receptores. Anteriormente se han descrito inhibidores de la angiogénesis relacionados con VEGFR y TIE-2 en relación con los inhibidores de la transducción de señales (ambos son tirosina quinasas asociadas a receptores). Pueden usarse otros inhibidores en combinación con los compuestos de la invención. Por ejemplo, también pueden resultar útiles en combinación con los compuestos de la invención anticuerpos anti-VEGF que no reconocen VEGFR (la tirosina quinasa asociada a receptores), pero se unen al ligando; inhibidores de molécula pequeña de integrina ($\alpha_v\beta_3$) que inhiben la angiogénesis; endostatina y angiostatina (no-RTK). Un ejemplo de un anticuerpo contra VEGFR es bevacizumab (AVASTIN®).

Están en desarrollo varios inhibidores de receptores de factores de crecimiento e incluyen antagonistas de ligandos, anticuerpos, inhibidores de tirosina

quinasa, oligonucleótidos antisentido y aptámeros. Cualquiera de estos inhibidores de receptores de factores de crecimiento puede emplearse en combinación con los compuestos de la invención en cualquiera de las composiciones y métodos/ usos descritos en la presente memoria. El trastuzumab (Herceptin®) es un ejemplo de un anticuerpo anti-erbB2 inhibidor de la función de factores de crecimiento. Un ejemplo de un anticuerpo anti-erbB1 inhibidor de la función de factores de crecimiento es cetuximab (Erbix™, C225). El bevacizumab (Avastin®) es un ejemplo de un anticuerpo monoclonal dirigido contra VEGFR. Los ejemplos de inhibidores de molécula pequeña de receptores del factor de crecimiento epidérmico incluyen, pero sin limitación, lapatinib (Tykerb™) y erlotinib (TARCEVA®). El mesilato de imatinib (GLEEVEC®) es un ejemplo de un inhibidor de PDGFR. Los ejemplos de inhibidores de VEGFR incluyen pazopanib, ZD6474, AZD2171, PTK787, sunitinib y sorafenib. Son de interés particular el pazopanib y los compuestos de fórmula I y sus sales.

Los agentes anti-microtúbulos o anti-mitóticos son agentes con especificidad de fase activos contra los microtúbulos de células tumorales durante la fase M o la fase de mitosis del ciclo celular. Los ejemplos de agentes anti-microtúbulos incluyen, pero sin limitación, diterpenoides y alcaloides de la vinca.

Los diterpenoides, que proceden de fuentes naturales, son agentes anticancerosos con especificidad de fase que funcionan en las fases G₂/M del ciclo celular. Se piensa que los diterpenoides estabilizan la subunidad de β-tubulina de los microtúbulos por unión con esta proteína. Después parece inhibirse el desensamblaje de la proteína, deteniéndose la mitosis y siguiendo la muerte celular. Los ejemplos de diterpenoides incluyen, pero sin limitación, paclitaxel y su análogo docetaxel.

El paclitaxel, 4,10-diacetato-2-benzoato-13-éster de 5β,20-epoxi-1,2α,4,7β,10β,13α-hexa-hidroxitax-11-en-9-ona con (2R, 3S)-N-benzoil-3-fenilisoserina; es un producto de diterpeno natural aislado a partir del tejo del Pacífico *Taxus brevifolia*, y está disponible en el mercado como una solución inyectable conocida como TAXOL®. Es un miembro de la familia de terpenos conocida como taxanos. Se aisló por primera vez en 1971 por Wani et al. (J. Am. Chem. Soc., 93: 2325. 1971), que caracterizaron su estructura por métodos químicos y cristalográficos de rayos X. Un mecanismo para su actividad se refiere a la capacidad del paclitaxel para unirse a la tubulina, inhibiendo de este modo el desarrollo de células cancerosas. Schiff et al., Proc. Natl. Acad. Sci. USA, 77: 1561-

- 1565 (1980); Schiff et al., *Nature*, 277: 665-667 (1979); Kumar, J. *Biol. Chem.*, 256: 10435-10441 (1981). Para una revisión de la síntesis y actividad anticancerosa de algunos derivados de paclitaxel véase: D.G.I. Kingston *et al.*, *Studies in Organic Chemistry* vol. 26, titulado "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

El paclitaxel se ha autorizado para uso clínico en el tratamiento del cáncer de ovario resistente a tratamiento en los Estados Unidos (Markman et al., *Yale Journal of Biology and Medicine*, 64: 583, 1991; McGuire et al., *Ann. Intern. Med.*, 111: 273, 1989) y para el tratamiento de cánceres de mama (Holmes et al., *J. Nat. Cancer Inst.*, 83: 1797, 1991). Es un posible candidato para el tratamiento de neoplasmas en la piel (Einzig et. al., *Proc. Am. Soc. Clin. Oncol.*, 20:46) y carcinomas de cabeza y cuello (Forastire et. al., *Semin. Oncol.*, 20: 56, 1990). El compuesto también muestra potencial para el tratamiento de la enfermedad renal poliquística (Woo et. Al., *Nature*, 368: 750, 1994), cáncer de pulmón y malaria. El tratamiento de pacientes con paclitaxel ocasiona supresión de la médula ósea (múltiples linajes celulares, Ignoff, R.J. et. al, *Cancer Chemotherapy Pocket Guide*, 1998) relacionada con la duración de la dosificación por encima de una concentración umbral (50 nM) (Kearns, CM et. al., *Seminars in Oncology*, 3(6) p. 16-23, 1995).

El docetaxel, 13-éster de éster N-*terc*-butílico de (2R,3S)-N-carboxi-3-fenilisoserina con 4-acetato-2-benzoato de 5 β -20-epoxi-1,2 α ,4,7 β ,10 β ,13 α -hexahidroxitax-11-en-9-ona trihidrato, está disponible en el mercado como una solución inyectable conocida como TAXOTERE®. El docetaxel está indicado para el tratamiento de cánceres de mama. El docetaxel es un derivado semisintético del paclitaxel, véase anteriormente, preparado usando un precursor natural, 10-desacetil-bacatina III, extraído de la acícula del tejo europeo. La toxicidad limitante de la dosis del docetaxel es la neutropenia.

Los alcaloides de la vinca son agentes antineoplásicos con especificidad de fase derivados de la planta vincapervinca. Los alcaloides de la vinca actúan en la fase M (mitosis) del ciclo celular uniéndose específicamente a la tubulina. Por consiguiente, la molécula de tubulina unida no puede polimerizarse en microtúbulos. Se piensa que la mitosis se detiene en la metafase produciéndose posteriormente la muerte celular. Los ejemplos de alcaloides de la vinca incluyen, pero sin limitación, vinblastina, vincristina y vinorelbina.

La vinblastina, sulfato de vincaleucoblastina, está disponible en el mercado

como VELBAN® como una solución inyectable. Aunque tiene una indicación posible como terapia de segunda línea de diversos tumores sólidos, está indicada principalmente en el tratamiento del cáncer testicular y diversos linfomas incluyendo la enfermedad de Hodgkin; y linfomas linfocíticos e histiocíticos. La mielosupresión es el efecto secundario limitante de la dosis de la vinblastina.

La vincristina, 22-oxo-sulfato de vincaleucoblastina, está disponible en el mercado como ONCOVIN® como una solución inyectable. La vincristina está indicada para el tratamiento de leucemias agudas y también ha encontrado utilidad en regímenes de tratamiento para linfomas malignos de Hodgkin y no Hodgkin. Los efectos secundarios más comunes de la vincristina son alopecia y efectos neurológicos y en menor grado se producen efectos de mielosupresión y mucositis gastrointestinal.

La vinorelbina, 3',4'-dideshidro-4'-desoxi-C'novincaleucoblastina [R-(R*,R*)-2,3-dihidroxi-butanodioato (1:2) (sal)], disponible en el mercado como una solución inyectable de tartrato de vinorelbina (NAVELBINE®), es un alcaloide de la vinca semisintético. La vinorelbina está indicada como un agente único o en combinación con otros agentes quimioterapéuticos tales como cisplatino en el tratamiento de diversos tumores sólidos, particularmente cáncer pulmonar no microcíticos, de mama avanzado y de próstata que no responde a tratamiento con hormonas. La mielosupresión es el efecto secundario limitante de la dosis más común de la vinorelbina.

Los complejos de coordinación de platino son agentes anticancerosos sin especificidad de fase que interaccionan con el ADN. Los complejos de platino entran en las células tumorales, experimentan acuación y forman entrecruzamientos intra- e intercatenarios con el ADN causando efectos biológicos adversos en el tumor. Los ejemplos de complejos de coordinación de platino incluyen, pero sin limitación, cisplatino y carboplatino.

El cisplatino, cis-diaminodicloroplatino, está disponible en el mercado como PLATINOL® como una solución inyectable. El cisplatino está indicado principalmente en el tratamiento de cáncer testicular y ovárico metastásico y cáncer de vejiga avanzado. Los efectos secundarios limitantes de la dosis principales del cisplatino son nefrotoxicidad, que puede controlarse mediante hidratación y diuresis, y ototoxicidad.

El carboplatino, diamino [1,1-ciclobutano-dicarboxilato(2-)-O,O'] de platino está disponible en el mercado como PARAPLATIN® como una solución inyectable.

El carboplatino está indicado principalmente en el tratamiento de primera y segunda línea del carcinoma de ovario avanzado. La supresión de la médula ósea es la toxicidad limitante de la dosis del carboplatino.

Los agentes alquilantes son agentes anticancerosos sin especificidad de fase y electrófilos fuertes. Típicamente, los agentes alquilantes forman enlaces covalentes, por alquilación, con el ADN a través de restos nucleófilos de la molécula de ADN tales como grupos fosfato, amino, sulfhidrilo, hidroxilo, carboxilo e imidazol. Dicha alquilación altera la función del ácido nucleico ocasionando la muerte celular. Los ejemplos de agentes alquilantes incluyen, pero sin limitación, mostazas nitrogenadas tales como ciclofosfamida, melfalán y clorambucilo; alquil sulfonatos tales como busulfán; nitrosoureas tales como carmustina; y triacenos tales como dacarbazina.

La ciclofosfamida, 2-óxido de 2-[bis(2-cloroetil)amino]tetrahydro-2H-1,3,2-oxazafosforina monohidrato está disponible en el mercado como una solución inyectable o comprimidos conocidos como CYTOXAN®. La ciclofosfamida está indicada como un agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de linfomas malignos, mieloma múltiple y leucemias. Los efectos secundarios limitantes de la dosis más comunes de la ciclofosfamida son alopecia, náuseas, vómitos y leucopenia.

El melfalán, 4-[bis(2-cloroetil)amino]-L-fenilalanina, está disponible en el mercado como una solución inyectable o comprimidos conocidos como ALKERAN®. El melfalán está indicado para el tratamiento paliativo del mieloma múltiple y el carcinoma epitelial no resecable. La supresión de la médula ósea es el efecto secundario limitante de la dosis más común del melfalán.

El clorambucilo, ácido 4-[bis(2-cloroetil)amino]bencenobutanoico, está disponible en el mercado como comprimidos LEUKERAN®. El clorambucilo está indicado para el tratamiento paliativo de leucemia linfática crónica y linfomas malignos tales como linfoma folicular gigante y enfermedad de Hodgkin. La supresión de la médula ósea es el efecto secundario limitante de la dosis más común del clorambucilo.

El busulfán, dimetanosulfonato de 1,4-butanodiol, está disponible en el mercado como comprimidos MYLERAN®. El busulfán está indicado para el tratamiento paliativo de la leucemia mielógena crónica. La supresión de la médula ósea es el efecto secundario limitante de la dosis más común del busulfán.

La carmustina, 1,3-[bis(2-cloroetil)-1-nitrosourea, está disponible en el

mercado como viales individuales de material liofilizado como BiCNU®. La carmustina está indicada para el tratamiento paliativo como agente único o en combinación con otros agentes para tumores cerebrales, mieloma múltiple, enfermedad de Hodgkin y linfomas no-Hodgkin. La mielosupresión retardada es el efecto secundario limitante de la dosis más común de la carmustina.

La dacarbazina, 5-(3,3-dimetil-1-triazeno)-imidazol-4-carboxamida, está disponible en el mercado como viales individuales de material conocido como DTIC-Dome®. La dacarbazina está indicada para el tratamiento del melanoma maligno metastásico, y en combinación con otros agentes para el tratamiento de segunda línea de la enfermedad de Hodgkin. Los efectos secundarios limitantes de la dosis más comunes de la dacarbazina son náuseas, vómitos y anorexia.

Los antibióticos antineoplásicos son agentes sin especificidad de fase que se unen o se intercalan con el ADN. Típicamente, dicha acción produce complejos de ADN estables o una rotura de la cadena que altera la función normal de los ácidos nucleicos conduciendo a la muerte celular. Los ejemplos de agentes antineoplásicos antibióticos incluyen, pero sin limitación, actinomicinas tales como dactinomicina, antraciclinas tales como daunorubicina y doxorubicina; y bleomicinas.

La dactinomicina, también conocida como actinomicina D, está disponible en el mercado en forma inyectable como COSMEGEN®. La dactinomicina está indicada para el tratamiento del tumor de Wilm y el rabdomiosarcoma. Los efectos secundarios limitantes de la dosis más comunes de la dactinomicina son náuseas, vómitos y anorexia.

La daunorubicina, hidrocloreuro de (8S-cis)-8-acetil-[(3-amino-2,3,6-tridesoxi- α -L-lixo-hexopiranosil)oxi]-7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxi-5,12-naftacenodiona, está disponible en el mercado como una forma inyectable liposomal conocida como DAUNOXOME® o como un inyectable conocido como CERUBIDINE®. La daunorubicina está indicada para la inducción de remisión en el tratamiento de leucemia no linfocítica aguda y sarcoma de Kaposi asociado con VIH avanzado. La mielosupresión es el efecto secundario limitante de la dosis más común de la daunorubicina.

La doxorubicina, hidrocloreuro de (8S,10S)-10-[(3-amino-2,3,6-tridesoxi- α -L-lixo-hexopiranosil)oxi]-8-glicolil, 7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxi-5,12-naftacenodiona, está disponible en el mercado como una forma inyectable conocida como RUBEX® o ADRIAMYCIN RDF®. La doxorubicina está indicada

principalmente para el tratamiento de la leucemia linfoblástica aguda y de la leucemia mieloblástica aguda, pero también es un componente útil en el tratamiento de algunos tumores sólidos y linfomas. La mielosupresión es el efecto secundario limitante de la dosis más común de la doxorubicina.

5 La bleomicina, una mezcla de antibióticos glicopeptídicos citotóxicos aislados a partir de una cepa de *Streptomyces verticillus*, está disponible en el mercado como BLENOXANE®. La bleomicina está indicada como un tratamiento paliativo, como un agente único o en combinación con otros agentes, del carcinoma de células escamosas, linfomas y carcinomas testiculares. Los efectos secundarios
10 limitantes de la dosis más comunes de la bleomicina son toxicidades pulmonares y cutáneas.

Los inhibidores de la topoisomerasa II incluyen, pero sin limitación, epipodofilotoxinas.

15 Las epipodofilotoxinas son agentes antineoplásicos con especificidad de fase derivados de la mandrágora. Las epipodofilotoxinas afectan típicamente a células en las fases S y G₂ del ciclo celular por formación de un complejo ternario con la topoisomerasa II y el ADN causando roturas de la cadena de ADN. Las roturas de la cadena se acumulan y se produce la muerte celular. Los ejemplos de epipodofilotoxinas incluyen, pero sin limitación, etopósido y tenipósido.

20 El etopósido, 9[4,6-O-(R)-etiliden-β-D-glucopiranosido] de 4'-desmetil-epipodofilotoxina, está disponible en el mercado como una solución inyectable o cápsulas con el nombre VePESID® y se conoce comúnmente como VP-16. El etopósido está indicado como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de cáncer testicular y pulmonar no microcítico.
25 La mielosupresión es el efecto secundario más común del etopósido. La incidencia de leucopenia tiende a ser más grave que la trombocitopenia.

El tenipósido, 9[4,6-O-(R)-teniliden-β-D-glucopiranosido] de 4'-desmetil-epipodofilotoxina, está disponible en el mercado como una solución inyectable con el nombre VUMON® y se conoce comúnmente como VM-26. El tenipósido está
30 indicado como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda en niños. La mielosupresión es el efecto secundario limitante de la dosis más común del tenipósido. El tenipósido puede inducir tanto leucopenia como trombocitopenia.

Los agentes neoplásicos antimetabolito son agentes antineoplásicos con
35 especificidad de fase que actúan en la fase S (síntesis de ADN) del ciclo celular

inhibiendo la síntesis de ADN o inhibiendo la síntesis de bases de purina o pirimidina y limitando de esta manera la síntesis de ADN. Por consiguiente, la fase S no avanza y se produce la muerte celular. Los ejemplos de agentes antineoplásicos antimetabolito incluyen, pero sin limitación, fluorouracilo, metotrexato, citarabina, mecapurina, tioguanina y gemcitabina.

El 5-fluorouracilo, 5-fluoro-2-(1H,3H)pirimidinadiona, está disponible en el mercado como fluorouracilo. La administración de 5-fluorouracilo conduce a la inhibición de la síntesis de timidilato y también se incorpora tanto en el ARN como en el ADN. El resultado típicamente es la muerte celular. El 5-fluorouracilo está indicado como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de carcinomas de mama, colon, recto, estómago y páncreas. Los efectos secundarios limitantes de la dosis de 5-fluorouracilo son mielosupresión y mucositis. Otros análogos de fluoropirimidina incluyen 5-fluorodesoxiuridina (floxuridina) y monofosfato de 5-fluorodesoxiuridina.

La citarabina, 4-amino-1-β-D-arabinofuranosil-2(1H)-pirimidinona, está disponible en el mercado como CYTOSAR-U® y se conoce comúnmente como Ara-C. Se piensa que la citarabina presenta especificidad de fase celular en la fase S inhibiendo la elongación de cadena de ADN por incorporación terminal de citarabina en la cadena de ADN en crecimiento. La citarabina está indicada como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. Otros análogos de citidina incluyen 5-azacitidina y 2',2'-difluorodesoxicitidina (gemcitabina). La citarabina induce leucopenia, trombocitopenia y mucositis.

La mercaptopurina, 1,7-dihidro-6H-purina-6-tiona monohidrato, está disponible en el mercado como PURINETHOL®. La mercaptopurina presenta especificidad de fase celular en la fase S inhibiendo la síntesis de ADN mediante un mecanismo aún no especificado. La mercaptopurina está indicada como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. La mielosupresión y la mucositis gastrointestinal son los efectos secundarios esperados de la mercaptopurina a altas dosis. Un análogo de mercaptopurina útil es la azatioprina.

La tioguanina, 2-amino-1,7-dihidro-6H-purina-6-tiona, está disponible en el mercado como TABLOID®. La tioguanina presenta especificidad de fase celular en la fase S inhibiendo la síntesis de ADN mediante un mecanismo aún no especificado. La tioguanina está indicada como agente único o en combinación con

otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. El efecto secundario limitante de la dosis más común de la administración de tioguanina es mielosupresión, incluyendo leucopenia, trombocitopenia y anemia. Sin embargo, se producen efectos secundarios gastrointestinales y pueden ser limitantes de la dosis.

- 5 Otros análogos de purina incluyen pentostatina, eritrohidroxinoniladenina, fosfato de fludarabina y cladribina.

La gemcitabina, monohidrocloreto de 2'-desoxi-2',2'-difluorocitidina (isómero β) está disponible en el mercado como GEMZAR®. La gemcitabina presenta especificidad de fase celular en la fase S y bloqueo del avance de las células a través del límite G1/S. La gemcitabina está indicada en combinación con cisplatino en el tratamiento de cáncer pulmonar no microcítico localmente avanzado y en solitario en el tratamiento de cáncer pancreático localmente avanzado. El efecto secundario limitante de la dosis más común de la administración de gemcitabina es mielosupresión, incluyendo leucopenia, trombocitopenia y anemia.

- 15 El metotrexato, ácido N-[4[[[(2,4-diamino-6-pteridil)metil]metilamino]benzoil]-L-glutámico está disponible en el mercado como metotrexato sódico. El metotrexato presenta efectos de fase celular específicamente en la fase S inhibiendo la síntesis, reparación y/o replicación del ADN por medio de la inhibición de la ácido dihidrofólico reductasa que es necesaria para la síntesis de nucleótidos de purina y timidilato. El metotrexato está indicado como agente único o en combinación con otros agentes quimioterapéuticos en el tratamiento de coriocarcinoma, leucemia meníngea, linfoma no-Hodgkin y carcinomas de mama, cabeza, cuello, ovario y vejiga. Los efectos secundarios esperados de la administración de metotrexato son mielosupresión (leucopenia, trombocitopenia y anemia) y mucositis.

Las camptotecinas, incluyendo camptotecina y derivados de camptotecina, están disponibles o en desarrollo como inhibidores de la topoisomerasa I. Se cree que la actividad citotóxica de las camptotecinas está relacionada con su actividad inhibidora de la topoisomerasa I. Los ejemplos de camptotecinas incluyen, pero sin limitación, irinotecán, topotecán y las diversas formas ópticas de 7-(4-metilpiperazino-metilen)-10,11-etilendioxi-20-camptotecina descritas a continuación.

- 30 El irinotecán HCl, hidrocloreto de (4S)-4,11-dietil-4-hidroxi-9-[(4)-piperidinopiperidino]carboniloxi]-1H-pirano [3',4',6,7]indolizino[1,2-b]quinolina-3,14 (4H,12H)-diona, está disponible en el mercado como una solución inyectable
35 CAMPTOSAR®.

El irinotecán es un derivado de camptotecina que se une, junto con su metabolito activo SN-38, al complejo de topoisomerasa I - ADN. Se piensa que la citotoxicidad se produce como resultado de roturas irreparables de la doble cadena causadas por la interacción de la topoisomerasa I: ADN: irinotecán o complejo ternario SN-38 con enzimas de la replicación. El irinotecán está indicado para el tratamiento del cáncer metastásico de colon o de recto. Los efectos secundarios limitantes de la dosis del irinotecán HCl son mielosupresión, incluyendo neutropenia, y efectos GI incluyendo diarrea.

El topotecán HCl, monohidrocloreto de (S)-10-[(dimetilamino)metil]-4-etil-4,9-dihidroxi-1H-pirano[3',4',6',7']indolizino[1,2-b]quinolina-3,14-(4H,12H)-diona está disponible en el mercado como la solución inyectable HYCAMTIN®. El topotecán es un derivado de la camptotecina que se une al complejo de topoisomerasa I - ADN y evita la religación de roturas de cadenas sencillas producida por la topoisomerasa I en respuesta a la tensión de torsión de la molécula de ADN. El topotecán está indicado para el tratamiento de segunda línea del carcinoma metastásico del cáncer de ovario y pulmonar microcítico. El efecto secundario limitante de la dosis del topotecán HCl es mielosupresión, principalmente neutropenia.

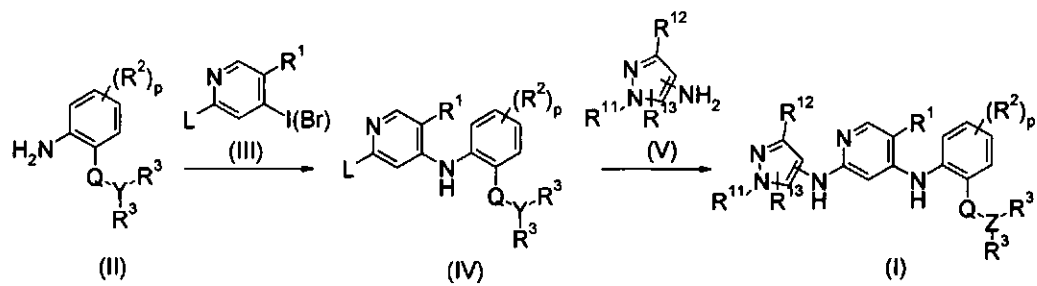
Los siguientes esquemas ilustran cómo pueden prepararse compuestos de la presente invención. Los disolventes y condiciones de reacción específicas indicadas también son ilustrativas y no pretenden ser limitantes.

Esquemas

Los compuestos de fórmula (I) pueden prepararse por los métodos que se indican a continuación en el Esquema 1. Los compuestos de fórmula (II) y (III) están disponibles en el mercado o pueden sintetizarse usando técnicas convencionales en la técnica. El grupo L para el compuesto (III) representa un grupo saliente tal como F o Cl. Los compuestos de fórmula (II) y (III) pueden hacerse reaccionar a la temperatura de reflujo o en condiciones de microondas para producir el intermedio (IV). La reacción de adición se realiza típicamente usando disolventes próticos polares tales como *n*-butanol o iso-propanol. Como alternativa, pueden usarse condiciones de reacción de acoplamiento catalizada con un metal. Cuando el compuesto (II) incluye un grupo funcional que necesita protección, por ejemplo, un grupo hidroxilo o amino, ventajosamente se usa un grupo protector apropiado. Los compuestos de fórmula (IV) pueden hacerse reaccionar después con un aminopirazol (V), que está disponible en el mercado o que puede sintetizarse usando técnicas convencionales en la técnica, para producir un compuesto de

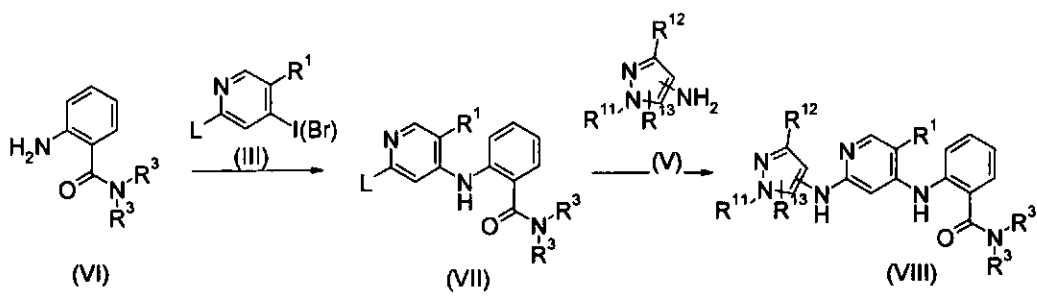
fórmula (I). La reacción se realiza típicamente en presencia de un catalizador de metal, tal como una sal de paladio, junto con un ligando de fosfina apropiado. Como alternativa, la reacción puede realizarse con una cantidad catalítica de un ácido tal como ácido clorhídrico o trifluoroacético y en un disolvente adecuado tal como agua, 1,4-dioxano o iso-propanol o una combinación de los mismos; la reacción se realiza ventajosamente a una temperatura elevada, por ejemplo, en condiciones de calentamiento a reflujo, o usando un aparato de microondas. El catalizador ácido está presente típicamente en una cantidad de 10-30% en moles con respecto al compuesto de fórmula (I).

10 Esquema 1



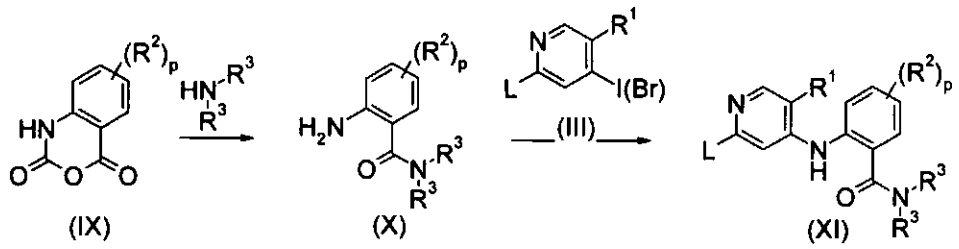
Los compuestos de fórmula (VIII) pueden prepararse convenientemente por los métodos indicados en el Esquema 1, pero partiendo con una antranilamida (VI) apropiada, como se indica en el Esquema 2.

15 Esquema 2



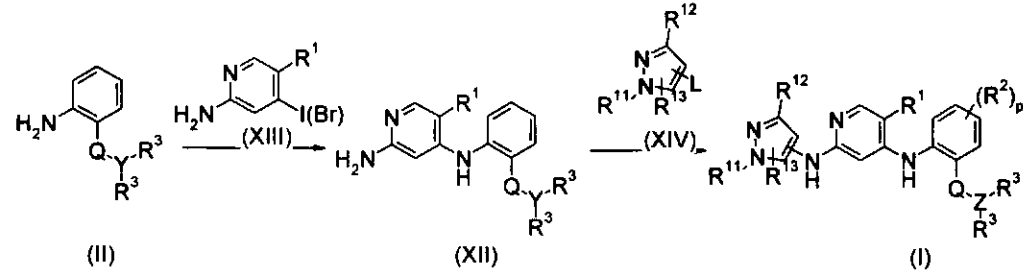
El compuesto (VI) puede contener sustituyentes adicionales. Por ejemplo, como se muestra en el Esquema 3, la benzoxazina (IX), que está disponible en el mercado o se sintetiza usando técnicas convencionales en la técnica, puede someterse a apertura del anillo con una amina para formar la benzamida (X), que después puede experimentar una adición con el compuesto (III) para producir el compuesto de fórmula (XI).

Esquema 3



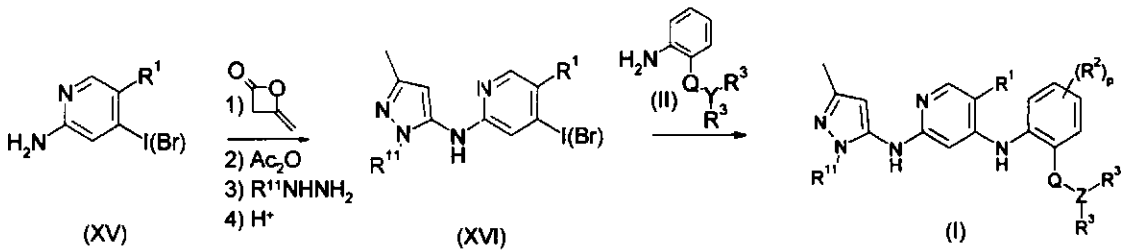
Un compuesto de fórmula (XII) puede prepararse haciendo reaccionar un compuesto de fórmula (II) con un compuesto de fórmula (XIII). Esta reacción puede realizarse como se ha descrito en el Esquema 1. Después, los compuestos de fórmula (XII) pueden hacerse reaccionar con un compuesto de fórmula (XIV) para dar compuestos de fórmula (I). La reacción puede realizarse en un disolvente inerte, en presencia de un catalizador de metal y un ligando apropiado.

Esquema 4



Algunos compuestos de fórmula (I) también pueden prepararse como se indica en el Esquema 5. El grupo amino del compuesto de fórmula (XV) puede hacerse reaccionar primero con diceteno seguido de acilación y tratamiento con una hidrazina. Después, el compuesto de fórmula (XVI) puede obtenerse por tratamiento con ácido y después hacerse reaccionar con un compuesto de fórmula (II) para dar un compuesto de fórmula (I). Esta última reacción puede realizarse como se describe en el Esquema 1.

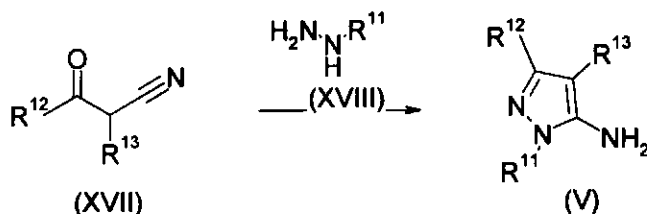
Esquema 5



Los compuestos de fórmula (V) pueden prepararse por condensación de una hidrazina sustituida (XVIII) con la ciano-cetona apropiada (XVII), por ejemplo, de acuerdo con los procedimientos de Honma, T. *et al. J. Med. Chem.* 2002, Vol. 44

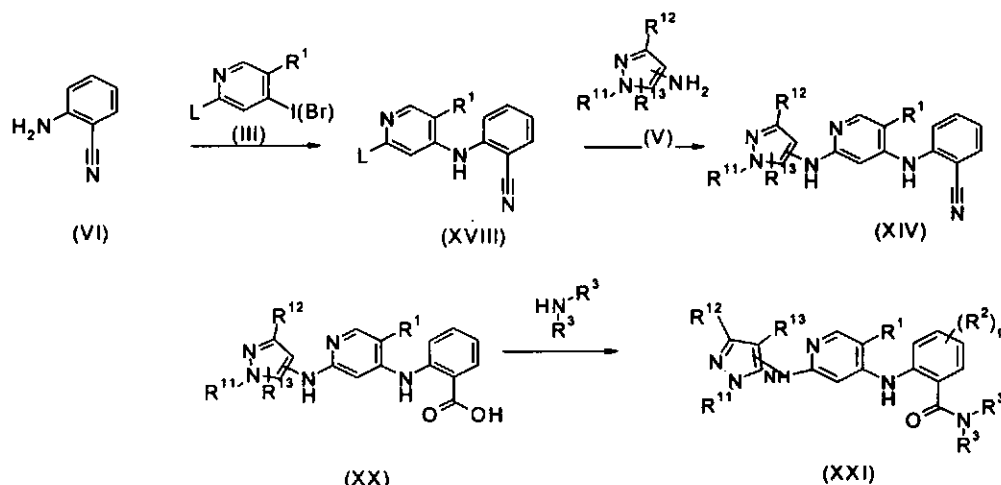
(26), 4628-4640 o Adachi, I. et al. *Chemical & Pharmaceutical Bulletin* **1987**, 35(8), 3235-52 como se muestra en el Esquema 6.

Esquema 6



5 Esquema 7

Un compuesto de fórmula (XXI) también puede prepararse como se muestra en el Esquema 7. El nitrilo de fórmula (XIV) puede hidrolizarse para dar un ácido carboxílico de fórmula (XX) y después acoplarse con una amina para dar compuestos de fórmula (XXI).



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PARTE EXPERIMENTAL

Ensayo bioquímico de la actividad de la FAK

Ensayo 1: Se adquirió FAK marcada con GST (marcada con glutatión S-transferasa) en Invitrogen (PV3832) (www.invitrogen.com). La actividad de FAK se midió por control de la fosforilación de un sustrato peptídico (Ac-RRRRRRSETDDYAEIID-NH₂; (SEC ID N° 1), es decir, Ac-Arg-Arg-Arg-Arg-Arg-Ser-Glu-Thr-Asp-Asp-Tyr-Ala-Glu-Ile-Ile-Asp-NH₂) en presencia de un ATP radiomarcado. Para medir los inhibidores de FAK, se prepararon primero compuestos como una solución madre 10 x en DMSO al 10%. Se añadió una pequeña porción de cada solución (4 µl) a una placa de 96 pocillos (Corning, 3884). Se preparó una solución de GST-FAK 6 nM en tampón de reacción 1,1x que contenía HEPES 44 mM, pH = 7,2, MgCl₂ 11 mM, MnCl₂ 2,2 mM, DTT 1,1 mM y Tween-20 al 0,011%. Después, se preincubaron 20 µl de la solución de GST-FAK 6

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nM con los compuestos durante 30 min a temperatura ambiente. La reacción se inició por adición de 16 µl de sustratos (péptido 62,5 µM, ATP 5 µM y ³³P-γ-ATP a ~0,02 mCi/ml) preparados en el tampón de reacción anterior. Se dejó que la reacción continuara durante 90 min antes de interrumpirse con 40 µl de H₃PO₄ al 1%. Una porción de la mezcla de reacción (60 µl) se transfirió a una placa con filtro de fosfo-celulosa (Millipore; www.millipore.com, MAPHNOB50) y se incubó durante 20 minutos. La placa se filtró, se lavó tres veces usando 150 µl de H₃PO₄ al 0,5% y se secó a 50°C durante 30 min. Después de la adición de 60 µl de Microscint-20 a la placa, se midió la radiactividad usando un TopCount (PerkinElmer, www.PerkinElmer.com).

Ensayo 2: Se preparó Flag-His-TEV-FAK1 en el laboratorio. Se expresó FAK humana de longitud completa usando baculovirus en células Sf9 con marcadores FLAG-6xHis N-terminales seguido de un sitio de escisión TEV (FLAG-6xHis-TEV-huFAK). La actividad de FAK se midió monitorizando la fosforilación del sustrato LANCE Ultra NH₂-(ULight)-CSETDDYAEIID-COOH (SEC ID N°: 2) (C = cisteína, S = serina, E = ácido glutámico, T = treonina, D = ácido aspártico, Y = tirosina, A = alanina, I = isoleucina) (adquirido en Perkin Elmer Life Sciences). Para medir inhibidores de FAK, se prepararon primero compuestos como una solución madre 100X en DMSO al 100%. Una pequeña porción de cada solución de compuesto (50 nl) se añadió a una placa de microtitulación de volumen reducido de 384 pocillos negros (Greiner 784076). Se preparó una solución de Flag-His-TEV-FAK1 1,2 nM en tampón de reacción 1X que contenía Tris/Tris-HCl 40 mM, MgCl₂ 10 mM, CHAPS 1 mM a un pH de 7,5, con DTT 1 mM añadido. Se añadieron 2,5 µl de la solución de Flag-FAK 1,2 nM a las placas y se preincubaron con los compuestos durante 30 min a temperatura ambiente. Después se añadieron 2,5 µl de solución de sustrato (0,1 µM de sustrato específico P2 FAK-tide (Lance Ultra NH₂-(ULight)-CSETDDYAEIID-COOH (SEC ID N°: 2) de Perkin Elmer), ATP 10 µM y el tampón de reacción 1x descrito anteriormente) a la placa para iniciar la reacción. Después de incubar durante 120 minutos a temperatura ambiente, la reacción se interrumpió por la adición de 5 µl de EDTA 20 mM y anticuerpos Eu-anti-pTyr 5 nM en tampón de detección LANCE 1X. Después de una incubación de 30 minutos a temperatura ambiente, la placa se leyó en un Perkin Elmer Viewlux con un filtro de excitación a 320-340 nm y se midió la emisión a 615 nm y 665 nm. La proporción de 665 nm/615 nm se usa para la normalización de los datos.

La siguiente Tabla A proporciona datos específicos para compuestos de los

ejemplos presentados a continuación procesados en uno o los dos ensayos anteriores. Estos datos se generaron en al menos un proceso en el ensayo indicado; los procesos de ensayo repetidos pueden haber proporcionado o pueden dar lecturas que varían en cierto grado de estos datos.

5 Tabla A

Ejemplo N°	Ensayo 1 FAK TRF PXC ₅₀	Ensayo 2 FAK H 31284A TRF PXC ₅₀
1	8,7	7,8
2	8,8	8
3	9,2	8,3
4	9	8,2
5	9	8,1
6	8,9	8,3
7	9,1	8
8	9,2	8,3
9	9	8,2
10	9,1	8
11	8,7	8,2
12	8,6	8,3
13	9,3	8,7
14	8,6	7,7
15	8,6	7,7
16	8,9	7,7
17	8,9	7,4
18	8	
19	8,3	7,2
20	8	7,4
21	8,5	7,2
22	7,5	6,6
23	7,1	6,7
24	8,2	7,2
25	8,6	7,5
26	9,4	8,4
27	8,7	8,1

77

Ejemplo N°	Ensayo 1 FAK TRF PXC ₅₀	Ensayo 2 FAK H 31284A TRF PXC ₅₀
28	9,4	8,6
29	9,3	8,7
30	9,4	8,8
31	8,4	
32	9,4	9
33	9,4	
34	9,3	
36	9,4	8,8
37	8,4	7,7
38	6,6	6
39	9,4	8,3
40	8,9	8,6
41	9,4	8,7
42	7,9	7,3
43	8,3	7,6
44	8,2	7,2
45	8	7,2
46		7,9
47		8,6
49		7,2
50		7,9
51		7,7
52		8,2
53		7,4
54		7,5
55		8
56		7,8
58		7,3
59	9,2	8,3
60		7,9
61		7,6
62		

Ejemplo N°	Ensayo 1 FAK TRF PXC ₅₀	Ensayo 2 FAK H 31284A TRF PXC ₅₀
63		7,3
64		7,1
65		7,8
66	8,7	7,5
67	7,2	8,3
69		8,6
70		8,2
71		8,2
72		8,6
73		8,9

Ejemplos Químicos

Los siguientes ejemplos químicos tienen propósitos ilustrativos y no pretenden limitar el alcance de la presente invención. Los compuestos se nombraron usando el programa informático ACD Name (Advanced Chemistry Development, www.acdlabs.com). Todos los compuestos tienen un valor de pCl₅₀ mayor que 6,5 para el ensayo bioquímico descrito anteriormente.

Se hizo funcionar un espectrómetro de masas de cuadrupolo único PE Sciex API 150 (PE Sciex, Thornhill, Ontario, Canadá) usando ionización por electronebulización en el modo de detección de iones positivos. El gas de nebulización se generó a partir de un generador de aire cero (Balston Inc., Haverhill, MA; www.parker.com) y se suministró a 448,16 kPa (65 psi) y el gas protector era nitrógeno de alta pureza suministrado desde un recipiente de nitrógeno líquido Dewar a 344,74 kPa (50 psi). El voltaje aplicado a la aguja de electronebulización fue de 4,8 kV. el orificio se ajustó a 25 V y el espectrómetro de masas se examinó a una velocidad de 0,5 exploraciones/seg usando una masa de etapa de 0,2 amu y recolección de datos de perfil.

Método A, LCMS. Se introducen muestras en el espectrómetro de masas usando un automuestreador CTC PAL (LEAP Technologies, Carrboro, NC) equipado con una jeringa hamilton de 10 µl que realizó la inyección en una válvula de inyección Valco de 10 puertos. La bomba de HPLC era una Shimadzu LC-10ADvp (Shimadzu Scientific Instruments, Columbia, MD) accionada a 0,3 ml/min y con un gradiente lineal de 4,5% de A a 90% de B en 3,2 min con un mantenimiento

de 0,4 min. La fase móvil se componía de 100% de (H₂O con TFA al 0,02%) en el recipiente A y 100% de (CH₃CN con TFA al 0,018%) en el recipiente B. La fase estacionaria es Aquasil (C18) y las dimensiones de la columna son 1 mm x 40 mm. La detección se realizó por UV a 214 nm, dispersión de luz evaporativa (ELSD) y MS.

Método B, LCMS. Como alternativa, se usó un sistema de HPLC analítica Agilent 1100 con una LC/MS y se accionó a 1 ml/min con un gradiente lineal de 5% de A a 100% de B en 2,2 min con un mantenimiento de 0,4 min. La fase móvil se componía de 100% de (H₂O con TFA al 0,02%) en el recipiente A y 100% de (CH₃CN con TFA al 0,018%) en el recipiente B. La fase estacionaria fue Zobax (C8) con un tamaño de partículas de 3,5 µm y las dimensiones de la columna fueron 2,1 mm x 50 mm. La detección se realizó por UV a 214 nm, dispersión de luz evaporativa (ELSD) y MS.

Método B, LCMS. Como alternativa, se usó un MDSSCIEX API 2000 equipado con una columna capilar de (50 x 4,6 mm, 5 µm). El análisis por HPLC se realizó en un sistema de UPLC Agilent-1200 series equipado con una columna Zorbax SB-C18 (50 x 4,6 mm, 1,8 µm) eluyendo con CH₃CN:tampón acetato de amonio. Las reacciones se realizaron en el microondas (CEM, Discover).

Los espectros de ¹H RMN (en lo sucesivo "RMN") se registraron a 400 MHz usando un instrumento Bruker AVANCE 400 MHz, usando un administrador ACD Spect ver. 10 para el reprocesamiento. Las multiplicidades indicadas son: s = singlete, d = doblete, t = triplete, c = cuadruplete, m = multiplete, dd = doblete de dobletes, dt = doblete de tripletes, etc y a indica una señal ancha.

HPLC analítica: Los productos se analizaron por un sistema de Cromatografía Analítica Agilent 1100, con una columna Zorbax XDB-C18 de 4,5 x 75 mm (3,5 µm) a 2 ml/min con un gradiente de 4 min de CH₃CN al 5% (ácido fórmico al 0,1%) a CH₃CN al 95% (ácido fórmico al 0,1%) en H₂O (ácido fórmico al 0,1%) y un mantenimiento de 1 min.

HPLC preparativa: Los productos se purificaron usando un sistema de cromatografía preparativa Gilson con una columna YMC CombiPrep ODS-A de 75 x 30 mm de D.I. (5 µm) (www.aguas.com) a 50 ml/min con un gradiente de 10 min de CH₃CN al 5% (ácido fórmico al 0,1%) a CH₃CN al 95% (ácido fórmico al 0,1%) en H₂O (ácido fórmico al 0,1%) y un mantenimiento de 2 min; como alternativa, los productos se purificaron usando un sistema de Cromatografía Preparativa Agilent 1100, con una columna Gemini C18 de 100 x 30 mm (5 µm) a 60 ml/min con un

gradiente de 10 min de CH₃CN al 5% (ácido fórmico al 0,1%) a CH₃CN al 95% (ácido fórmico al 0,1%) en H₂O (ácido fórmico al 0,1%) y un mantenimiento de 2 min.

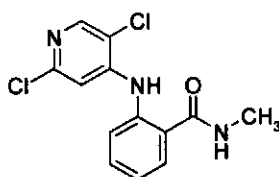
La cromatografía preparativa de fase normal se realizó usando un Sistema Analogix IntelliFlash 280 con columnas SuperFlash Septra Si 50. Como alternativa, la HPLC de fase inversa se realizó en Agilent usando una columna Zorbax SB - C18 (21,2 x 250 mm, 7 mm) eluyendo con CH₃CN:tampón acetato de amonio (10 µM) a pH 6,8.

Ejemplos

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Ejemplo 1

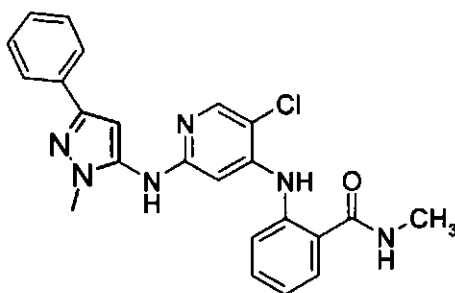
1a) 2-[(2,5-Dicloro-4-piridinil)amino]-N-metilbenzamida



Un tubo de 150 ml cerrado herméticamente se cargó con 2,5-dicloro-4-yodopiridina (3,5 g, 12,78 mmol), 2-amino-N-metilbenzamida (1,919 g, 12,78 mmol) y fosfato tripotásico (8,14 g, 38,3 mmol) en 1,4-dioxano (100 ml). La mezcla de reacción se desgasificó con nitrógeno durante 10 min. Se añadieron bis(2-difenilfosfinofenil)éter (DPEPhos, 0,688 g, 1,278 mmol) y Pd(OAc)₂ (0,115 g, 0,511 mmol) y la mezcla de reacción se calentó en un baño de aceite a 120°C durante una noche. La mezcla de reacción se filtró a través de celite, que se lavó con dioxano. El disolvente se evaporó a sequedad y el sólido se lavó con EtOH (10 ml x 3) para dar 2,14 g (56%) de producto en forma de un sólido de color blanquecino.

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1b) 2-[5-Cloro-2-(2-metil-5-fenil-2H-pirazol-3-il-amino)-piridin-4-il-amino]-N-metil-benzamida



Un tubo de 50 ml cerrado herméticamente se cargó con Pd(OAc)₂ (18 mg, 0,08 mmol) y 2,2'-bis(difenilfosfino)-1,1'-binaftilo (BINAP, 50 mg, 0,08 mmol) en 1,4-dioxano (10 ml). La mezcla se desgasificó usando burbujeo de nitrógeno durante 40

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min y se calentó a 50°C durante 1 h. Después, la mezcla se enfrió a temperatura ambiente, después de lo cual se añadieron 2-[(2,5-dicloro-4-piridinil)amino]-N-metilbenzamida (300 mg, 1,01 mmol), 2-metil-5-fenil-2H-pirazol-3-il-amina (704 mg, 4,06 mmol) y carbonato de cesio (960 mg, 2,96 mmol) en una atmósfera inerte. El tubo se cerró herméticamente y se calentó a 120°C durante una noche. La mezcla de reacción se concentró a presión reducida y el producto en bruto se purificó por cromatografía en columna (gel de sílice, eluyendo con 99:1 de diclorometano-metanol (DCM-MeOH) seguido de purificación por TLC preparativa para producir el compuesto deseado en forma de un sólido de color blanquecino (25 mg, 5%). ¹H RMN (400 MHz, DMSO-*d*₆) δ 2,76 (d, 3H, *J* = 4,52 Hz), 3,68 (s, 3H), 6,69 (s, 1H), 6,85 (s, 1H), 7,07-7,14 (m, 1H), 7,25-7,31 (m, 1H), 7,36-7,42 (m, 2H), 7,46-7,53 (m, 1H), 7,63 (d, 1H, *J* = 8,08 Hz), 7,69 (d, 1H, *J* = 7,4 Hz), 7,75 (d, 2 H, *J* = 7,16 Hz), 8,04 (s, 1H), 8,69 (s, 1H), 8,81 (s, 1H), 10,13 (s, 1H). LC-MS calculado para C₂₃H₂₁ClN₆O (M + H) 433,15, encontrado 433,3. Pureza de HPLC de 96% en λ = 200 nm y de 99% en λ = 260 nm.

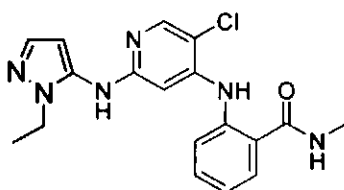
Ejemplo 2

2-[(5-Cloro-2-[(1-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida

Una mezcla de 2-[(2,5-dicloro-4-piridinil)amino]-N-metilbenzamida (100 mg, 0,338 mmol), 5-amino-1-metil-1H-pirazol (65,6 mg, 0,675 mmol), Cs₂CO₃ (220 mg, 0,675 mmol), tris(dibencilidenoacetona)dipaladio (Pd₂(dba)₃, 61,8 mg, 0,068 mmol) y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (Xantphos, 48,8 mg, 0,084 mmol) se calentó a 150°C en un horno de microondas durante 30 min. La mezcla de reacción se filtró, el filtrado se concentró, el producto en bruto resultante se purificó por HPLC de fase inversa y el producto se trató con HCl 2 N para dar 34 mg de producto en forma de una sal HCl (24%). LCMS (ES) *m/z* = 357,1 (M+H); ¹H RMN (400 MHz, metanol-*d*₄) δ ppm 8,01 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,61 (m, 2H), 7,55 (d, *J* = 2 Hz, 1H), 7,42-7,39 (m, 1H), 6,52 (s, 1H), 6,33 (d, *J* = 2 Hz, 1H), 3,76 (s, 3H), 2,91 (s, 3H).

Ejemplo 3

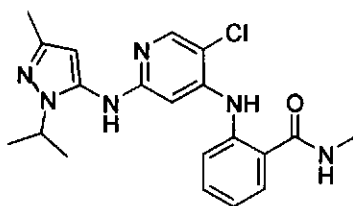
2-[(5-Cloro-2-[(1-etil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida



El compuesto del título se preparó sustancialmente como se ha descrito en el Ejemplo 2 con la excepción de que se usó 5-amino-1-etil-1H-pirazol en lugar de 5-amino-1-metil-1H-pirazol. LCMS (ES) m/z = 371,1 (M+H); ^1H RMN (400 MHz, METANOL- d_4) δ ppm 8,06 (m, 1H), 7,77-7,61 (m, 4H), 7,44-7,40 (m, 1H), 6,61 (m, 1H), 6,40 (s, 1H), 4,17-4,10 (m, 2H), 2,91 (s, 3H), 1,40 (tr, J = 7,2 Hz, 3H).

Ejemplo 4

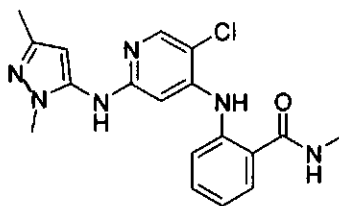
2-[(5-Cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida



El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 2 con la excepción de que se usó 5-amino-1-isopropilpropilpropil-1H-pirazol en lugar de 5-amino-1-metil-1H-pirazol. LCMS (ES) m/z = 399,2 (M+H); ^1H RMN (400 MHz, metanol- d_4) δ ppm 8,06 (s, 1H), 7,78-7,76 (m, 1H), 7,65-7,63 (m, 2H), 7,45-7,38 (m, 1H), 6,64 (s, 1H), 6,29 (s, 1H), 4,70-4,55 (m, 1H), 2,91 (s, 3H), 2,34 (s, 1H), 1,47 (d, J = 6,8 Hz, 6H).

Ejemplo 5

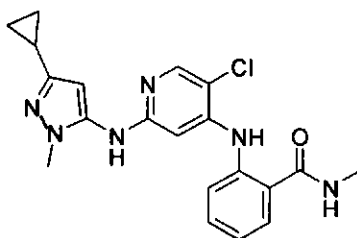
2-[(5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida



El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 2 con la excepción de que se usó 5-amino-1-metil-3-metil-1H-pirazol en lugar de 5-amino-1-metil-1H-pirazol. LCMS (ES) m/z = 371,1 (M+H); ^1H RMN (400 MHz, metanol- d_4) δ ppm 8,12 (s, 1H), 7,78-7,76 (d, J = 7,6 Hz, 1H), 7,66-7,64 (m, 2H), 7,45-7,41 (m, 1H), 6,67 (s, 1H), 6,38 (s, 1H), 3,80 (s, 3H), 2,91 (s, 3H), 2,35 (s, 3H).

Ejemplo 6

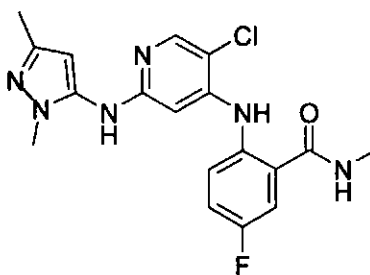
2-[(5-Cloro-2-[(3-ciclopropil-1-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida



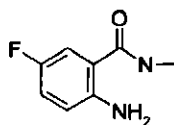
El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 2 con la excepción de que se usó 5-amino-3-ciclopropil-1-metil-1H-pirazol en lugar de 5-amino-1-metil-1H-pirazol. LCMS (ES) $m/z = 397,1$ (M+H); ^1H RMN (400 MHz, metanol- d_4) δ ppm 8,06 (s, 1H), 7,78-7,76 (m, 1H), 7,64-7,62 (m, 2H), 7,44-7,40 (m, 1H), 6,57 (s, 1H), 6,15 (s, 1H), 3,71 (s, 3H), 2,91 (s, 3H), 1,97-1,90 (m, 1H), 1,04-1,00 (m, 2H), 0,79-0,76 (m, 2H).

Ejemplo 7

2-((5-Cloro-2-((1,3-dimetil-1H-pirazol-5-il)amino)-4-piridinil)amino)-5-fluoro-N-metilbenzamida



7a) 2-Amino-5-fluoro-N-metilbenzamida



Se disolvió 6-fluoro-2H-3,1-benzoxazina-2,4(1H)-diona (200 mg, 1,104 mmol) en tetrahidrofurano seco (THF) (10 ml), momento en el que se añadió metil amina (3,31 ml, 6,63 mmol). La reacción se agitó a temperatura ambiente durante 1 h y después se concentró al vacío. El producto en bruto se purificó sobre sílice (Biotage, EtOAc al 40%/hexano) para producir el compuesto del título (120 mg, 65%) en forma de un sólido de color blanco. LC-MS (ES) $m/z = 169,1$ (M+H)⁺

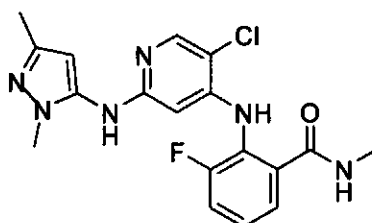
7b) 2-((5-Cloro-2-((1,3-dimetil-1H-pirazol-5-il)amino)-4-piridinil)amino)-5-fluoro-N-metilbenzamida

El compuesto del título se preparó en forma de un sólido de color blanco haciendo reaccionar primero 2-amino-5-fluoro-N-metilbenzamida con 2,5-dicloro-4-yodopiridina para formar 2-((2,5-dicloro-4-piridinil)amino)-5-fluoro-N-metilbenzamida

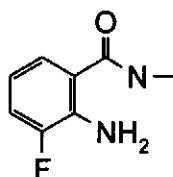
sustancialmente de acuerdo con el procedimiento del Intermedio 1 y después haciendo reaccionar este intermedio con 1,3-dimetil-1H-pirazol-5-amina sustancialmente de acuerdo con el procedimiento del Ejemplo 2. LC-MS (ES) m/z = 389,1 (M+H)⁺, ¹H RMN (CD₃OD, 400 MHz) δ 8,01 (s, 1H), 7,60 (m, 1H), 7,51 (m, 1H), 7,38 (m, 1H), 6,39 (s, 1H), 6,18 (s, 1H), 3,69 (s, 3H), 2,89 (s, 3H), 2,24 (s, 3H)

Ejemplo 8

2-({5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-3-fluoro-N-metilbenzamida



8a) 2-Amino-3-fluoro-N-metilbenzamida



Se disolvió 2-amino-3-fluorobenzonitrilo (3,8 g, 27,9 mmol) en etanol, agua (15 ml) y THF (0,3 ml) y se añadió hidróxido potásico (7,83 g, 140 mmol). La mezcla se calentó a 85°C durante 12 h, se enfrió y se filtró. El filtrado se concentró y el residuo se disolvió en diclorometano (DCM, 50 ml). Después, se añadió diisopropiletilamina (19,50 ml, 112 mmol) seguido de metil amina (20,94 ml, 41,9 mmol) y hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP, 21,79 g, 41,9 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se lavó con salmuera y se secó sobre MgSO₄. El disolvente se retiró y el residuo se purificó por cromatografía sobre gel de sílice (EtOAc al 20%/Hex) para dar 1,5 g (rendimiento de 35%) del intermedio a.

8b). 2-({5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-3-fluoro-N-metilbenzamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 7, con la excepción de que se usó 2-amino-3-fluoro-N-metilbenzamida en lugar de 2-amino-5-fluoro-N-metilbenzamida: LC-MS (ES) m/z = 389,1 (M+H)⁺, ¹H RMN (CD₃OD, 400 MHz) δ 8,01 (s, 1H), 7,50 (m, 3H), 6,14 (s, 1H), 5,87 (m, 1H), 3,65 (s, 3H), 2,89 (s, 3H), 2,22 (s, 3H)

Los compuestos de 2-[[5-cloro-2-(amino pirazol)-4-piridinil]amino]-benzamida que se ilustran en la Tabla 1 se prepararon a partir de diversas 2-[(2,5-dicloro-4-piridinil)amino]-metilbenzamidas y amino-pirazoles sustancialmente de acuerdo con el procedimiento del Ejemplo 7. En las tablas que se muestran a

5 continuación, las líneas de rayas indican los puntos de unión. Por lo tanto, para el Ejemplo 9, el compuesto corresponde a la siguiente estructura:

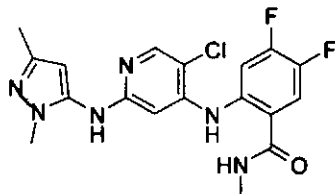
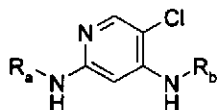
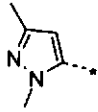
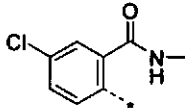
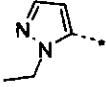
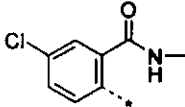
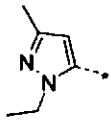
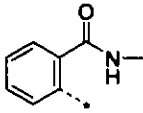
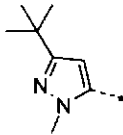
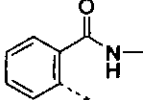


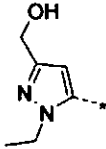
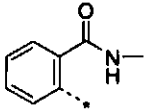
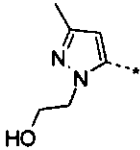
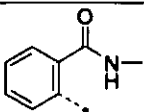
Tabla 1



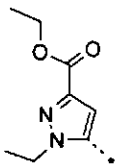
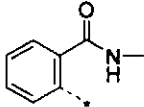
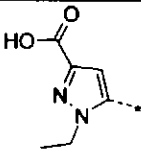
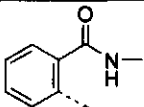
Ej.	Nombre	R _a	R _b	Datos
9	2-({5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-4,5-difluoro-N-metilbenzamida			LC-MS (ES) m/z = 407,1 (M+H) ⁺ , ¹ H RMN (CD ₃ OD, 400 MHz) d 8,04 (s, 1H), 7,71 (m, 1H), 7,61 (m, 1H), 6,63 (s, 1H), 6,28 (s, 1H), 3,72 (s, 3H), 2,89 (s, 3H), 2,72 (s, 3H)
10	2-({5-Cloro-2-[(1-etil-1H-pirazol-5-il)amino]-4-piridinil}amino)-4,5-difluoro-N-metilbenzamida			LC-MS (ES) m/z = 460,1 (M+H) ⁺ , ¹ H RMN (CD ₃ OD, 400 MHz) d 8,00 (s, 1H), 7,70 (m, 1H), 7,59

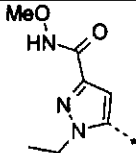
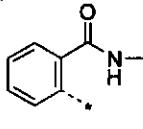
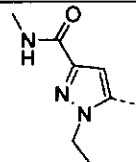
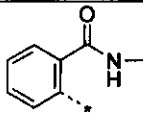
Ej.	Nombre	R _a	R _b	Datos
				(m, 2H), 6,56 (s, 1H), 6,33 (s, 1H), 4,11 (m, 2H), 2,90 (m, 3H), 1,38 (m, 3H)
11	5-Cloro-2-((5-cloro-2-((1,3-dimetil-1H-pirazol-5-il)amino)-4-piridinil)amino)-N-metilbenzamida			LC-MS (ES) m/z = 407,0 (M+H) ⁺ , ¹ H RMN (CD ₃ OD, 400 MHz) d 8,03 (s, 1H), 7,78 (m, 1H), 7,61 (m, 2H), 6,56 (s, 1H), 6,23 (s, 1H), 3,70 (s, 3H), 2,90 (s, 3H), 2,26 (s, 3H)
12	5-Cloro-2-((5-cloro-2-((1-etil-1H-pirazol-5-il)amino)-4-piridinil)amino)-N-metilbenzamida			LC-MS (ES) m/z = 407,0 (M+H) ⁺ , ¹ H RMN (CD ₃ OD, 400 MHz) d 8,00 (s, 1H), 7,78 (m, 1H), 7,59 (m, 3H), 6,50 (s, 1H), 6,32 (m, 1H), 4,10 (m, 2H), 2,89 (s, 3H), 1,37 (s, 3H)
13	2-((5-Cloro-2-((1-etil-3-metil-1H-pirazol-5-il)amino)-4-piridinil)amino)-N-metilbenzamida			LCMS (ES) m/z = 384,8 (M+H); ¹ H

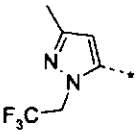
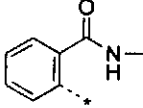
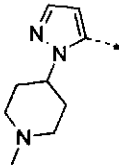
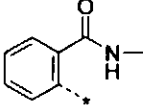
Ej.	Nombre	R _a	R _b	Datos
				RMN (400 MHz, METANOL- <i>d</i> ₄) <i>d</i> ppm 8,01 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,61 (m, 2H), 7,41-7,37 (m, 1H), 6,59 (s, 1H), 6,20 (s, 1H), 4,07-4,01 (m, 2H), 2,91 (s, 3H), 2,27 (s, 3H), 1,35 (tr, J = 7,2 Hz, 3H).
14	2-[(5-Cloro-2-[[3-(1,1-dimetil)-1-metil-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-metilbenzamida			LCMS (ES) <i>m/z</i> = 412,8 (M+H); 1H RMN (400 MHz, METANOL- <i>d</i> ₄) <i>d</i> ppm 8,05 (s, 1H), 7,75-7,72 (m, 1H), 7,60-7,58 (m, 2H), 7,40-7,35 (m, 1H), 6,52 (s, 1H), 6,27 (s, 1H), 3,70 (s, 3H), 2,91 (s, 3H), 1,30 (s, 9H).

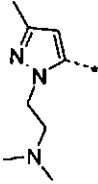
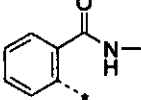
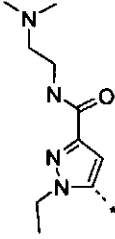
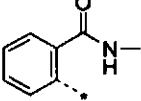
Ej.	Nombre	R _a	R _b	Datos
15	2-[(5-Cloro-2-[[1-etil-3-(hidroximetil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-metilbenzamida			LCMS (ES) m/z = 401,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 7,99 (s, 1H), 7,75-7,73 (m, 1H), 7,61-7,59 (m, 2H), 7,39- 7,35 (m, 1H), 6,58 (s, 1H), 6,31 (s, 1H), 4,56 (s, 2H), 4,08-4,03 (m, 2H), 2,91 (s, 3H), 1,36 (tr, J = 7,2 Hz, 6H).
16	2-[(5-Cloro-2-[[1-(2-hidroxietil)-3-metil-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-metilbenzamida			LCMS (ES) m/z = 401,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 8,07 (s, 1H), 7,78-7,76 (m, 1H), 7,65-7,63 (m, 2H), 7,43- 7,39 (m, 1H), 6,69 (s, 1H), 6,31 (s, 1H), 4,18 (tr, J = 5,2 Hz, 2H), 3,85 (tr, J = 5,2 Hz, 2H),

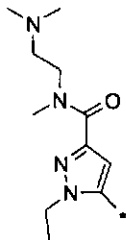
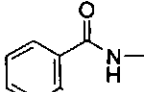
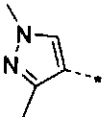
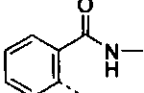
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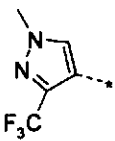
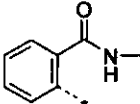
Ej.	Nombre	R _a	R _b	Datos
				2,91 (s, 3H), 2,32 (s, 3H).
17	5-[[5-Cloro-4-({2- [(metilamino)carbonil]fenil}amino)- 2-piridinil]amino]-1-etil-1H-pirazol- 3-carboxilato de etilo			LCMS (ES) m/z = 443,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 8,02 (s, 1H), 7,75-7,74 (m, 1H), 7,62-7,60 (m, 2H), 7,40- 7,36 (m, 1H), 6,82 (s, 1H), 6,59 (s, 1H), 4,41-4,36 (m, 2H), 4,19-4,14 (m, 2H), 2,91 (s, 3H), 1,43- 1,37 (m, 6H).
18	Ácido 5-[[5-cloro-4-({2- [(metilamino)carbonil]fenil}amino)- 2-piridinil]amino]-1-etil-1H-pirazol- 3-carboxílico			LCMS (ES) m/z = 415,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 8,02 (s, 1H), 7,78-7,76 (m, 1H), 7,65-7,63 (m, 2H), 7,44- 7,40 (m, 1H), 6,83 (s, 1H), 6,59 (s, 1H), 4,20-4,14 (m, 2H), 2,91 (s,

Ej.	Nombre	R _a	R _b	Datos
				3H), 1,42 (tr, J = 6,8 Hz, 3H).
19	5-[[5-Cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino)-1-etil-N-(metiloxi)-1H-pirazol-3-carboxamida			LCMS (ES) m/z = 444,1 (M+H); 1H RMN (400 MHz, METANOL-d ₄) d ppm 8,01 (s, 1H), 7,76-7,74 (m, 1H), 7,63-7,62 (m, 2H), 7,41-7,37 (m, 1H), 6,74 (s, 1H), 6,57 (s, 1H), 4,16-4,13 (m, 2H), 3,81 (s, 3H), 2,91 (s, 3H), 1,42 (tr, J = 6,8 Hz, 3H).
20	5-[[5-Cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino)-1-etil-N-metil-1H-pirazol-3-carboxamida			LCMS (ES) m/z = 428,1 (M+H); 1H RMN (400 MHz, METANOL-d ₄) d ppm 8,01 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,61 (m, 2H), 7,41-7,38 (m, 1H), 6,71 (s, 1H), 6,55 (s, 1H), 4,16-4,10 (c, J = 7,2 Hz, 2H),

Ej.	Nombre	R _a	R _b	Datos
				2,92 (s, 3H), 2,91 (s, 3H), 1,42 (tr, J = 7,2 Hz, 3H).
21	2-[(5-Cloro-2-[[3-metil-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-metilbenzamida			LCMS (ES) m/z = 439,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 8,00 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,58 (m, 2H), 7,40- 7,36 (m, 1H), 6,61 (s, 1H), 6,25 (s, 1H), 4,82-4,76 (c, J = 8,4 Hz, 2H), 2,91 (s, 3H), 2,27 (s, 3H).
22	2-[(5-Cloro-2-[[1-(1-metil-4-piperidinil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-metilbenzamida			LCMS (ES) m/z = 440,1 (M+H); 1H RMN (400 MHz, METANOL- d ₄) d ppm 8,04 (s, 1H), 7,75-7,73 (m, 1H), 7,61-7,57 (m, 3H), 7,42- 7,38 (m, 1H), 6,45 (s, 1H), 6,33 (s, 1H).

Ej.	Nombre	R _a	R _b	Datos
				4,60-4,50 (m, 1H), 3,67-3,63 (m, 2H), 3,25-3,15 (m, 2H), 2,91 (s, 3H), 2,90 (s, 3H), 2,40-2,12 (m, 4H).
23	2-[[5-Cloro-2-({1-[2-(dimetilamino)etil]-3-metil-1H-pirazol-5-il}amino)-4-piridinil]amino]-N-metilbenzamida			LCMS (ES) m/z = 428,1 (M+H); 1H RMN (400 MHz, METANOL-d4) d ppm 8,06 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,61 (m, 2H), 7,43-7,38 (m, 1H), 6,59 (s, 1H), 6,18 (s, 1H), 4,41-4,38 (t, J = 5,6 Hz, 2H), 3,63-3,60 (t, J = 5,6 Hz, 2H), 2,98 (s, 6H), 2,91 (s, 3H), 2,25 (s, 3H).
24	5-[[5-Cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-N-[2-(dimetilamino)etil]-1-etil-1H-pirazol-3-carboxamida			LCMS (ES) m/z = 485,2 (M+H); 1H RMN (400 MHz, METANOL-d4) d ppm 8,03 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,60 (m, 2H), 7,40-7,35 (m, 1H),

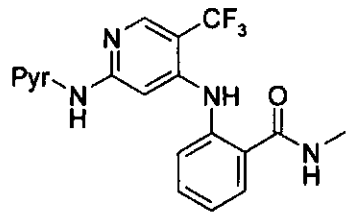
				6,76 (s, 1H), 6,56 (s, 1H), 4,16-4,14 (c, J = 7,2 Hz, 2H), 3,77 (tr, J = 6,0 Hz, 2H), 3,38 (tr, J = 6,0 Hz, 2H), 2,99 (s, 6H), 2,91 (s, 3H), 1,42 (tr, J = 7,2 Hz, 3H).
25	5-[[5-Cloro-4-((2-((metilamino)carbonil)fenil)amino)-2-piridinil]amino]-N-[2-(dimetilamino)etil]-1-etil-N-metil-1H-pirazol-3-carboxamida			LCMS (ES) m/z = 499,2 (M+H); 1H RMN (400 MHz, METANOL-d4) d ppm 8,04 (s, 1H), 7,76-7,74 (m, 1H), 7,62-7,60 (m, 2H), 7,40-7,35 (m, 1H), 6,70 (s, 1H), 6,52 (s, 1H), 4,16-4,10 (m, 2H), 3,95-3,90 (m, 1H), 3,58-3,40 (m, 5H), 3,20-3,15 (m, 1H), 3,03 (s, 6H), 2,91 (s, 3H), 1,42 (tr, J = 7,2 Hz, 3H).
26	2-((5-Cloro-2-((1,3-dimetil-1H-pirazol-4-il)amino)-4-piridinil)amino)-N-metilbenzamida			LC-MS (ES) m/z = 371,1 (M+H)+; 1H RMN (CD3OD, 400 MHz) d 7,88 (s, 1H), 7,84 (s, 1H), 7,75 (m, 1H), 7,64 (m, 2H),

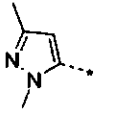
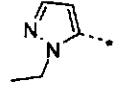
				7,40 (m, 1H), 6,58 (s, 1H), 3,92 (s, 3H), 2,92 (s, 3H), 2,18 (s, 3H)
27	2-({5-Cloro-2-[(1,3-dimetil-1H- pirazol-4-il)amino]-4- piridinil}amino)-N-metilbenzamida			LC-MS (ES) m/z = 425,0 (M+H) ⁺ , ¹ H RMN (CD ₃ OD, 400 MHz) d 7,98 (s, 1H), 7,90 (s, 1H), 7,76 (m, 1H), 7,63 (m, 2H), 7,40 (m, 1H), 6,58 (s, 1H), 4,00 (s, 3H), 2,91 (s, 3H)

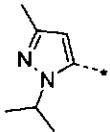
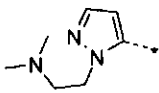
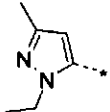
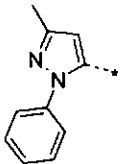
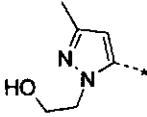
Los compuestos de 2-{{5-trifluorometil-2-(aminopirazol)-4-piridinil}amino}-benzamida ilustrados en la Tabla 2 se prepararon a partir de 2-[(2-cloro-5-trifluorometil-4-piridinil)amino]-metilbenzamida y el amino-pirazol correspondiente

5 sustancialmente de acuerdo con el procedimiento del Ejemplo 2.

Tabla 2

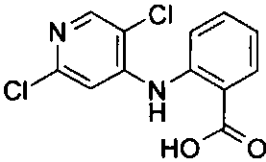


Ex	Nombre	Pir	Datos
28	2-[[2-[(1,3-Dimetil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida		LC-MS (ES) m/z = 405,1 (M+H) ⁺
29	2-[[2-[(1-Etil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida		LC-MS (ES) m/z = 405,1 (M+H) ⁺

Ex	Nombre	Pir	Datos
30	<i>N</i> -metil-2-[[2-[[3-metil-1-(1-metiletil)-1 <i>H</i> -pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]benzamida		LC-MS (ES) m/z = 433,2 ($M+H$) ⁺
31	2-[[2-[[1-[2-(Dimetilamino)etil]-3-metil-1 <i>H</i> -pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]- <i>N</i> -metilbenzamida		LC-MS (ES) m/z = 462,2 ($M+H$) ⁺
32	2-[[2-[[1-Etil-3-metil-1 <i>H</i> -pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]- <i>N</i> -metilbenzamida		LCMS (ES) m/z = 419,2 ($M+H$)
33	<i>N</i> -metil-2-[[2-[[3-metil-1-fenil-1 <i>H</i> -pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]benzamida		LCMS (ES) m/z = 467,1 ($M+H$)
34	2-[[2-[[1-(2-hidroxietil)-3-metil-1 <i>H</i> -pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]- <i>N</i> -metilbenzamida		LCMS (ES) m/z = 435,1 ($M+H$)

Intermedio 1

Ácido 2-[(2,5-dicloro-4-piridinil)amino]benzoico

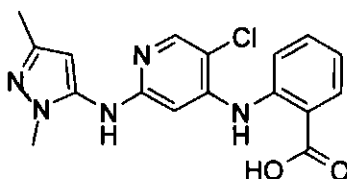


5 Una mezcla de 2,5-dicloro-4-yodopiridina (10 g, 36,5 mmol), ácido 2-aminobenzoico (4,85 g, 35,4 mmol), DPEPhos [bis(2-difenilfosfinofenil)éter] (1,6 g, 2,97 mmol), acetato de paladio (II) (160 mg, 0,713 mmol) y K₃PO₄ (20 g, 94 mmol) se desgasificó y se calentó a 120°C (temperatura del baño de aceite) durante 20 h.

Después de 20 h, el análisis LCMS mostró que aún quedaba 33% de material de partida (en relación con el producto deseado). A la mezcla se le añadieron 160 mg más de $\text{Pd}(\text{OAc})_2$ y se calentó a 120°C durante 24 h más. El LCMS mostró que la conversión se había completado. La mezcla se enfrió a temperatura ambiente
5 seguido de filtración, lavando con EtOAc. Los sólidos se acidificaron a $\text{pH} = 7-8$ seguido de filtración. Sin embargo, la mezcla era una pasta y los sólidos recogidos no pudieron secarse completamente. Los sólidos (11 g) se acidificaron con HCl 6 N a $\text{pH} = 1$. La pasta resultante se filtró y se lavó con agua y TBME. El sólido se secó al vacío sobre P_2O_5 durante 2 días para dar el compuesto del título (7,32 g,
10 rendimiento de 60,2%). MS: $\text{M}(\text{C}_{12}\text{H}_8\text{Cl}_2\text{N}_2\text{O}_2) = 283,11$, $(\text{M}+\text{H})^+ = 283,8$; ^1H RMN (400 MHz, DMSO) δ ppm 13,6 (s, 1 H) 10,2 (s, 1 H) 8,3 (s, 1 H) 8,0 (d, 1 H) 7,6 (c, 2 H) 7,3 (s, 1 H) 7,2 (m, 1 H).

Ejemplo 35

Ácido 2-([5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino)benzoico



15

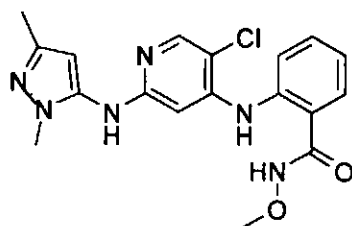
Un tubo a presión se cargó con ácido 2-[(2,5-dicloro-4-piridinil)amino]benzoico (1,0 g, 3,53 mmol), 1,3-dimetil-1H-pirazol-5-amina (0,589 g, 5,30 mmol), ($\pm$)-2,2'-Bis(difenilfosfino)-1,1'-binaftaleno (0,330 g, 0,530 mmol), tris(dibencilidenoacetona)dipaladio (0) ($\text{Pd}_2(\text{dba})_3$, 0,162 g, 0,177 mmol) y terc-butóxido sódico (0,849 g, 8,83 mmol) en 1,4-dioxano (30 ml). El tubo se desgasificó con N_2 , se cerró herméticamente y la mezcla de reacción se calentó en un baño de aceite a 120°C durante 18 horas. La mezcla de reacción se evaporó a sequedad a alto vacío. El residuo se recogió de nuevo en una solución agua y el pH se ajustó de ~ 4 a 5 usando ácido clorhídrico 6,0 N. La reacción se concentró a sequedad y el
20 sólido resultante se disolvió en MeOH y se purificó por HPLC de fase inversa para dar el compuesto del título en forma de un sólido (285 mg, rendimiento de 21%). MS: $\text{M}(\text{C}_{17}\text{H}_{16}\text{ClN}_5\text{O}_2) = 357,79$, $(\text{M}+\text{H})^+ = 358, 360$.

25

Ejemplo 36

2-([5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino)-N-(metiloxi)benzamida

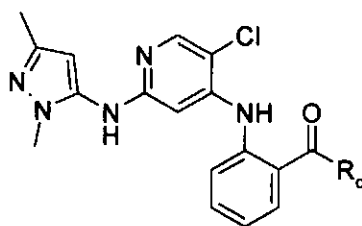
30



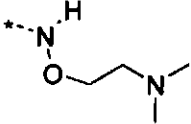
Un recipiente se cargó con ácido 3-((5-cloro-2-((1,3-dimetil-1H-pirazol-5-il)amino)-4-piridinil)amino)benzoico (100 mg, 0,279 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (53,6 mg, 0,279 mmol) e hidroxibenzotriazol (42,8 mg, 0,279 mmol) en N,N-dimetilformamida (DMF, 1,0 ml) y el contenido se agitó a temperatura ambiente durante 30 min. A esta mezcla se le añadió hidrocloreuro de metoxilamina (23,34 mg, 0,279 mmol) y la agitación se continuó durante 10 más. La mezcla de reacción se enfrió a 0°C. Se añadió diisopropiletilamina (DIEA, 0,098 ml, 0,559 mmol) y la mezcla de reacción se agitó a temperatura ambiente una noche. El material en bruto final se purificó usando HPLC de fase inversa, (Gilson) eluyendo con CH₃CN/H₂O con ácido fórmico al 0,1% para producir 15 mg (rendimiento de 18%) MS: M(C₁₈H₁₉ClN₆O₂) = 386,84, (M+H)⁺ = 387; ¹H RMN (400 MHz, MeOD) δ ppm 8,16 (s, 1 H) 7,93 (s, 1 H) 7,50 - 7,66 (m, 2 H) 7,11 - 7,25 (m, 1 H) 6,62 (s, 1 H) 5,99 (s, 1 H) 3,80 (s, 3 H) 3,55 - 3,70 (s, 3 H) 2,11 - 2,26 (s, 3 H).

Los compuestos de 2-((5-cloro-2-((1, 3-dimetil-1H-pirazol-5-il)amino)-4-piridinil) amino)-N-alquil-N-(alquililoxi)benzamida ilustrados en la Tabla 3 se prepararon a partir de ácido 3-((5-cloro-2-((1,3-dimetil-1H-pirazol-5-il)amino)-4-piridinil)amino)benzoico y amino-alcoholes sustancialmente de acuerdo con el procedimiento del Ejemplo 36.

Tabla 3

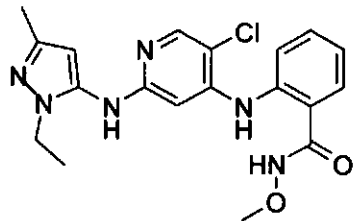


Ex	Nombre	R _c	Datos
37	2-((5-cloro-2-((1, 3-dimetil-1H-pirazol-5-il)amino)-4-piridinil) amino)-N-metil-N-		LC-MS (ES) m/z = 387 (M+H) ⁺ ; ¹ H RMN (400 MHz, MeOD) δ

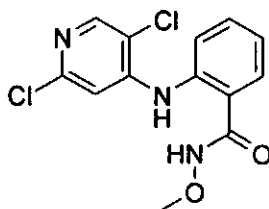
Ex	Nombre	R _c	Datos
	(metiloxi)benzamida		ppm 8,16 (s, 1 H) 7,93 (s, 1 H) 7,50 - 7,66 (m, 2 H) 7,11 - 7,25 (m, 1 H) 6,62 (s, 1 H) 5,99 (s, 1 H) 3,80 (s, 3 H) 3,55 - 3,70 (s, 3 H) 2,11 - 2,26 (s, 3 H)
38	2-({5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-{{2-(dimetilamino)etil}oxi}benzamida		LC-MS (ES) m/z = 444, 446 (M+H) ⁺ ; 1H RMN (400 MHz, MeOD) δ ppm 8,50 (s, 1 H) 7,93 (s, 1 H) 7,64 - 7,71 (m, 1 H) 7,51 - 7,61 (m, 2 H) 7,21 (ddd, J = 8,0, 6,2, 2,3 Hz, 1 H) 6,58 (s, 1 H) 5,98 (s, 1 H) 4,22 - 4,31 (m, 2 H) 3,61 (s, 3 H) 3,33 - 3,40 (m, 2H) 2,96 (s, 6 H) 2,19 (s, 3 H)

Ejemplo 39

2-({5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-(metiloxi)benzamida



39a) 2-[(2,5-Dicloro-4-piridinil)amino]-N-(metiloxi)benzamida



Un recipiente se cargó con ácido 3-[(2,5-dicloro-4-piridinil)amino]benzoico (1,0 g, 3,53 mmol), hidrocloreto de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (677 mg, 3,53 mmol) e hidroxibenzotriazol (HOBt) (541 mg, 3,53 mmol) en N,N-dimetilformamida (DMF, 7,0 ml) y se agitó a temperatura ambiente durante 30 min. A esta solución se le añadió hidrocloreto de metoxilamina (0,3 g, 3,53 mmol) y la mezcla de reacción se agitó durante 10 min más. La mezcla de reacción se enfrió a 0°C usando un baño de hielo. A esta mezcla de reacción se le añadió diisopropiletilamina (1,2 ml, 7,06 mmol) y la mezcla se agitó a temperatura ambiente una noche. Después de la concentración al vacío, el residuo se trató usando una solución acuosa saturada de NaHCO₃ y CH₂Cl₂. La fase orgánica se lavó con salmuera, después se secó sobre MgSO₄ y se filtró. El CH₂Cl₂ se retiró por evaporación rotatoria. El material en bruto se cargó sobre una columna de gel de sílice y se eluyó con MeOH en CH₂Cl₂ con NH₄OH al 0,1%, dando el producto deseado 2-[(2, 5-dicloro-4-piridinil) amino]-N-(metiloxi)benzamida (850 mg, 2,72 mmol, rendimiento de 77%) MS: M(C₁₃H₁₁Cl₂N₃O₂) = 312,15, (M+H)⁺ = 312, 314; ¹H RMN (400 MHz, CLOROFORMO-d) δ ppm 9,57 (s a, 1 H) 8,72 (s, 1 H) 8,22 (s, 1 H) 7,51 - 7,67 (m, 3H) 7,25 (s, 1 H) 7,07 - 7,21 (m, 1 H) 3,92 (s, 3 H).

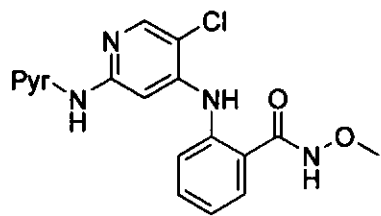
39b) 2-[(5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida

Un tubo para microondas de 20 ml se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (100 mg, 0,320 mmol), 1-etil-3-metil-1H-pirazol-5-amina (60,1 mg, 0,481 mmol), carbonato de cesio (313 mg, 0,961 mmol), 1,4-dioxano (5,0 ml) y THF (1,0 ml). La mezcla de reacción se desgasificó con nitrógeno durante 10 min. Después, se añadieron (±)-2,2'-bis(difenilfosfino)-1,1'-binaftaleno (19,95 mg, 0,032 mmol) y acetato de paladio (II) (3,60 mg, 0,016 mmol) en una cantidad mínima de 1,4-dioxano. El tubo se cerró herméticamente y la mezcla de reacción se calentó en un horno de microondas 160°C durante 40 min. La suspensión resultante se enfrió a temperatura ambiente y se filtró a través de celite. El filtrado se evaporó a sequedad y la mezcla de reacción en bruto se purificó por HPLC de fase inversa para dar el compuesto del título en forma de un sólido (16

mg, rendimiento del 24%) MS: $M(C_{19}H_{21}ClN_6O_2) = 400,86$, $(M+H)^+ = 401$; ^1H RMN (400 MHz, MeOD) δ ppm 7,92 (s, 1 H) 7,44 - 7,66 (m, 3 H) 7,11 - 7,25 (m, 1 H) 6,61 (s, 1 H) 5,99 (s, 1 H) 3,98 (c, $J = 7,3$ Hz, 2 H) 3,80 (s, 3 H) 2,21 (s, 3 H) 1,32 (t, $J = 7,2$ Hz, 3 H).

5 Los compuestos de 2-({5-cloro-2-(pirazol-5-il)amino}-4-piridinil)amino)-*N*-(metiloxi)benzamida ilustrados en la Tabla 4 se prepararon a partir de 2-[(2,5-dicloro-4-piridinil)amino]-*N*-(metiloxi)benzamida y amino-pirazoles sustancialmente de acuerdo con el procedimiento del Ejemplo 39.

Tabla 4

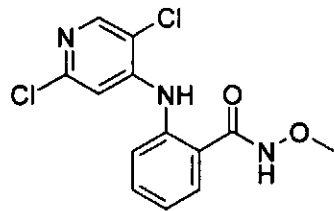


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Ex	Nombre	Pir	Datos
40	2-({5-Cloro-2-[(1-etil-1H-pirazol-5-il)amino]-4-piridinil}amino)- <i>N</i> -(metiloxi)benzamida		LC-MS (ES) $m/z = 387, 388$ $(M+H)^+$; ^1H RMN (400 MHz, MeOD) δ ppm 1H 7,90 - 7,96 (m, 1 H) 7,49 - 7,66 (m, 3 H) 7,45 (t, $J = 2,2$ Hz, 1 H) 7,10 - 7,22 (m, 1 H) 6,61 (s, 1 H) 6,19 (d, $J = 1,8$ Hz, 1 H) 4,06 (c, $J = 7,1$ Hz, 2 H) 3,80 (s, 3 H) 1,35 (t, $J = 7,2$ Hz, 3H)

Intermedio 2

2-[(2,5-Dicloro-4-piridinil)amino]-*N*-(metiloxi)benzamida



15

Una solución de ácido 3-[(2,5-dicloro-4-piridinil)amino]benzoico (500 mg, 1,766 mmol), *N*-(3-dimetilaminopropil)-*N'*-etilcarbodiimida (EDC) (339 mg, 1,766 mmol) y 1-hidroxibenzotriazol (HOBT) (270 mg, 1,766 mmol) en *N,N*-

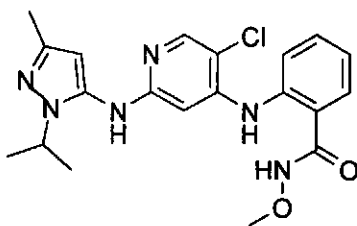
dimetilformamida (3532 ml) se agitó a temperatura ambiente durante 30 min. Después, a esta solución se le añadió O-metilhidroxilamina (aminoxi)metano (148 mg, 1,766 mmol) y se agitó durante 10 min más. La mezcla de reacción se enfrió usando un baño de agua enfriada con hielo. Después, se añadió

5 diisopropiletilamina (617 ml, 3,53 mmol). Después de que finalizara la adición, la mezcla de reacción se agitó a temperatura ambiente durante una noche. La mezcla de reacción se siguió por HPLC y LCMS. El material en bruto final se trató mediante la adición de NaHCO_3 acuoso saturado y CH_2Cl_2 . La fase orgánica se lavó con salmuera y después se secó sobre MgSO_4 . La solución se filtró y el disolvente se

10 retiró por evaporación. El aceite como material en bruto se cargó sobre una columna de sílice y se eluyó con MeOH en CH_2Cl_2 con NH_4OH al 0,1% para dar el compuesto diana 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (320 mg, 1,025 mmol, rendimiento de 58,0%) en forma de un sólido de color amarillo; MS; $\text{M}(\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_2) = 312,15$, $(\text{M}+\text{H})^+ = 312, 313,9$; ^1H RMN (400 MHz, CLOROFORMO- d) δ ppm 9,66 (s a, 1 H) 9,60 (s a, 1 H) 8,20 (s, 1 H) 7,49 - 7,61 (m, 3 H) 7,24 (s, 1 H) 7,09 - 7,16 (m, 1 H) 3,90 (s, 3 H).

Ejemplo 41a

2-[(5-Cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida



20

Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (70 mg, 0,224 mmol), {3-metil-1-(1-metiletil)-1H-pirazol-5-amina (70 mg, 0,503 mmol) y carbonato de cesio (230 mg, 0,706 mmol). La mezcla de reacción se desgasificó con nitrógeno durante 10 min. Al mismo tiempo, se

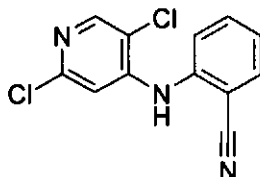
25 añadieron BINAP (50 mg, 0,080 mmol) y acetato de paladio (II) (10 mg, 0,045 mmol). La mezcla de reacción se calentó en un microondas a 160°C durante 40 min. El material en bruto se purificó por HPLC de fase inversa (Gilson) eluyendo con $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ con ácido fórmico al 0,1%, dando un compuesto del título (15 mg, 15%); MS: $\text{M}(\text{C}_{20}\text{H}_{23}\text{ClN}_6\text{O}_2) = 414,89$, $(\text{M}+\text{H})^+ = 415, 416$; ^1H RMN (400 MHz, CLOROFORMO- d) δ ppm 9,42 (s a, 1 H) 8,71 (s a, 1 H) 8,02 (s, 1 H) 7,54 (s a, 1 H) 7,06 (t, $J = 7,5$ Hz, 1 H) 6,48 (s, 1 H) 6,32 (s a, 1 H) 5,86 (s, 1 H) 4,47 (dt, $J = 13,4$,

30

6,7 Hz, 1 H) 3,92 (s, 3 H) 2,26 (s, 3 H) 1,41 - 1,43 (d, J = 6,6 Hz, 2H).

Intermedio 3

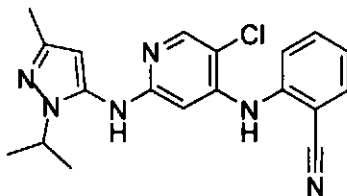
2-[(2,5-Dicloro-4-piridinil)amino]benzonitrilo



- 5 La solución de 2,5-dicloro-4-yodopiridina (100 g, 365 mmol), 2-aminobenzonitrilo (43,1 g, 365 mmol) y trifosfato potásico (233 g, 1095 mmol) en 1,4-dioxano (2,5 l) se desgasificó con una corriente de N₂. A esta solución se le añadieron DPEPhos (15,73 g, 29,2 mmol) y acetato de paladio (3,28 g, 14,60 mmol). La mezcla de reacción se agitó a la temperatura de reflujo durante 18 horas.
- 10 La solución se filtró a través de 1,27 cm (0,5 pul) de celite y 0,51 cm (0,2 pulgadas) de sílice. La solución se evaporó. El sólido se suspendió en el éter dietílico y se filtró. El éter dietílico se concentró y el sólido resultante se filtró. Se aisló 2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (80 g, 288 mmol, rendimiento de 79%) en forma de un sólido de color naranja. 1H RMN (400 MHz, DMSO-d₆) δ ppm 6,49 (s, 1 H)
- 15 7,50 (td, J = 7,58, 1,01 Hz, 1 H) 7,56 (d, J = 7,58 Hz, 1 H) 7,80 (td, J = 7,83, 1,77 Hz, 1 H) 7,95 (dd, J = 7,83, 1,52 Hz, 1 H) 8,26 (s, 1 H) 9,05 (s a, 1 H); HPLC Tr = 2,88 min, MS (ESI): 263,9, 265,9 [M+H]⁺.

Intermedio 4

2-[(5-Cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]benzonitrilo



- La solución de 2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (110 g, 396 mmol), 3-metil-1-(1-metiletil)-1H-pirazol-5-amina (55,1 g, 396 mmol) y carbonato de cesio (387 g, 1187 mmol) en 1,4-dioxano (2,5 l) se desgasificó con una corriente de
- 25 N₂ y se añadió 2,2'-bis(difenilfosfino)-1,1'-binaftilo (BINAP) (19,71 g, 31,7 mmol) seguido de acetato de paladio (3,55 g, 15,83 mmol). La mezcla de reacción se calentó a reflujo durante una noche en una atmósfera de N₂. La mezcla de reacción se filtró y el líquido se concentró. Se añadió acetato de etilo (1500 ml) seguido de

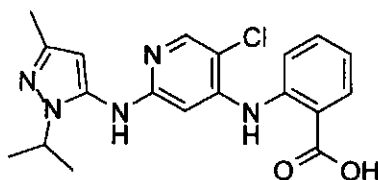
HCl 1 M (1000 ml). Las capas se separaron. El acetato de etilo se lavó con HCl 1 M hasta que no se observó producto por HPLC (1000 ml en total, 1 x). Las fases de HCl se combinaron y se lavaron de nuevo con acetato de etilo (3 x 1000 ml) hasta que el pico del producto era relativamente puro en la capa de HCl. Después, la

5 capa de HCl se basificó con NaOH (50 p/p seguido de 1 M) a pH ~4 dando como resultado una solución turbia. Se añadió acetato de etilo (2000 ml) y las capas se separaron. El acetato de etilo se lavó con salmuera y se evaporó. Después de la neutralización - tras la adición de acetato de etilo -, la mezcla de reacción se filtró para conseguir un poco de producto. Además, el aislamiento del producto durante

10 la evaporación puede realizarse por filtración del sólido de color blanco, que procede de las aguas madre. Todos los sólidos y productos evaporados se combinaron. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzonitrilo (80 g, 207 mmol, rendimiento de 52,4%) en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,24 (d, J = 6,57 Hz, 6 H) 2,08 (s, 3 H) 4,34 (quintuplete, J = 6,57 Hz, 1 H) 5,87 (s, 1 H) 5,97 (s, 1 H) 7,41 (td, J = 7,58, 1,01 Hz, 1 H) 7,47 (d, J = 8,08 Hz, 1 H) 7,75 (td, J = 7,83, 1,52 Hz, 1 H) 7,90 (dd, J = 7,83, 1,52 Hz, 1 H) 7,94 (s, 1 H) 8,42 (d, J = 17,43 Hz, 2 H); HPLC Tr = 2,36 min, MS (ESI): [M+H]⁺ = 367,1, 368,1.

Intermedio 5

20 Ácido 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzoico



Se disolvió 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzonitrilo (80 g, 218 mmol) en 1,4-dioxano (1,5 l) y se añadió

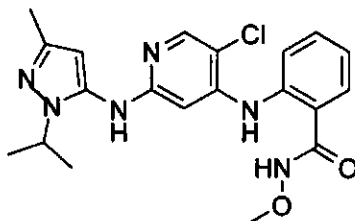
25 NaOH 1 M (1500 ml, 1500 mmol). La suspensión se calentó a reflujo durante una noche. Después de enfriar a TA, se añadió acetato de etilo (1 l) y las capas se separaron. La capa de agua se lavó con 1 l de acetato de etilo. Las dos capas orgánicas se combinaron y se lavaron de nuevo con NaOH 0,1 M (1 l) hasta que no se observó más cantidad de producto en la capa orgánica. Después, los productos

30 orgánicos se desecharon. Después, los productos acuosos combinados se lavaron con 1 l de acetato de etilo. Después, la capa de agua se acidificó con ácido acético (muy lentamente a pH ~ 7). El sólido se filtró y se aisló ácido 2-[(5-cloro-2-[[3-metil-

1-(1-metiletil)-1H-pirazol-5-il]amino}-4-piridinil)amino]benzoico (67 g, 165 mmol, rendimiento de 76%) en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,28 (d, J = 6,57 Hz, 6 H) 2,11 (s, 3 H) 4,41 (quintuplete, J = 6,57 Hz, 1 H) 5,96 (s, 1 H) 6,83 (s, 1 H) 7,09 (ddd, J = 8,02, 5,12, 3,03 Hz, 1 H) 7,40 (1 H) 7,52 - 7,61 (m, 2 H) 7,91 - 8,16 (m, 2 H) 8,55 (s, 1 H) 10,17 (s a, 1 H) 13,64 (s a, 1 H); HPLC Tr = 2,35 min, MS (ESI): [M+H]⁺ = 386,1.

Ejemplo 41b

2-[(5-Cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-N-(metiloxi)benzamida

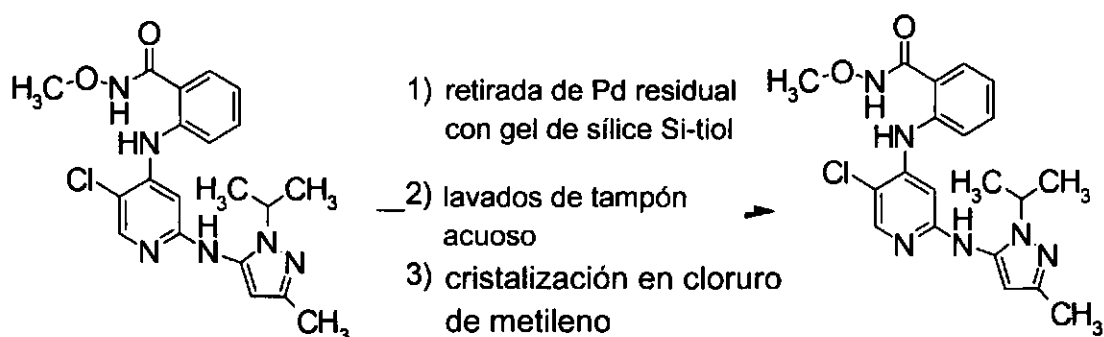


10

A una solución de ácido 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]benzoico (67 g, 174 mmol) y 1-hidroxibenzotriazol (29,3 g, 191 mmol) en N,N-dimetilformamida (700 ml) se le añadió N-(3-dimetilaminopropil)-N'-etilcarbodiimida (36,6 g, 191 mmol) y la solución se agitó durante 30 minutos. Se añadió hidrocloruro de O-metilhidroxilamina (15,95 g, 191 mmol) y la solución se agitó durante 15 minutos más, después la solución se enfrió a 0°C y se añadió gota a gota diisopropiletilamina (91 ml, 521 mmol). La mezcla de reacción se agitó durante una noche a la temperatura ambiente. Se añadió agua (4000 ml) y la solución se acidificó con ácido acético (20 ml). La solución se extrajo con 2 x 2 l de acetato de etilo. El producto orgánico se lavó con agua (1 l) y salmuera, se secó sobre MgSO₄, se filtró y se evaporó. Se aisló 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-N-(metiloxi)benzamida (74 g, 164 mmol, rendimiento de 94%, pureza de 92%) en forma de una espuma de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,27 (d, J = 6,57 Hz, 6 H) 2,10 (s, 3 H) 3,71 (s, 3 H) 4,39 (quintuplete, J = 6,51 Hz, 1 H) 5,93 (s, 1 H) 6,66 (s, 1 H) 7,08 - 7,19 (m, 1 H) 7,49 - 7,64 (m, 3 H) 7,98 (s, 1 H) 8,50 (s, 1 H) 9,50 (s, 1 H) 11,93 (s, 1 H); HPLC Tr = 2,13 min, MS (ESI): [M+H]⁺ = 415,1.

25

Purificación de los Productos del Ejemplo 41a y 41b



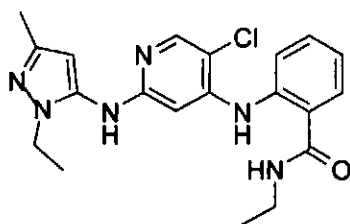
- Se disolvió 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-N-(metiloxi)benzamida (173,3 g, 63,5% de p/p, 265,2 mmol) en acetato de etilo (3,50 l, 20 volúmenes) y se calentó a aproximadamente 50°C. A esta solución se le añadió Si-tiol (gel de sílice funcionalizado) (87 g, carga al 50%). La mezcla se mantuvo a aproximadamente 50°C durante 16-20 horas. Después, el gel de sílice Si-tiol se retiró por filtración. La torta de filtro se aclaró con acetato de etilo (2 x 200 ml cada una) y los filtrados se combinaron. Después, los filtrados combinados se lavaron con formato de amonio acuoso 1 M a pH 9,4 (5 x 1 l cada uno), se lavaron con agua y salmuera y se secaron sobre sulfato de magnesio. El EtOAc seco se filtró y se extrajo a sequedad, dando una espuma de color amarillo. Se secó a 50-55°C durante aproximadamente 2 horas hasta alcanzar un peso constante de 160 g. Este material se suspendió en cloruro de metileno (800 ml, 5 volúmenes), se calentó a reflujo para producir una solución y se filtró. La solución se enfrió a 20-25°C. El producto cristalizó después de la refrigeración. Después de aproximadamente 2 horas, el producto se recogió por filtración y se aclaró con cloruro de metileno. El sólido de color blanco se secó a 50-55°C durante 14-16 horas hasta alcanzar un peso constante. Se aisló 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-N-(metiloxi)benzamida (85,0 g, 204,9 mmol, rendimiento global del 77%) en forma de un sólido de color blanco.
- ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,27 (d, J = 6,57 Hz, 6 H) 2,10 (s, 3 H) 3,70 (s, 3 H) 4,39 (quintuplete, J = 6,57 Hz, 1 H) 5,92 (s, 1 H) 6,66 (s, 1 H) 7,02-7,24 (m, 1 H) 7,45-7,68 (m, 3 H) 7,98 (s, 1 H) 8,48 (s, 1 H) 9,49 (s a, (s a, 1 H) 11,91 (s, 1 H). Tr de HPLC C18 = 6,2 minutos (pureza de 99,0%). MS (ESI): 415,0 [M+H]⁺.



Se suspendió 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida (235,2 g de peso total, 228,0 g de contenido ensayado, 549,5 mmol) en acetato de etilo (7,1 l, 30 volúmenes). La mezcla se calentó a aproximadamente 50-55°C para producir una solución turbia. La solución turbia se filtró. A la solución filtrada se le añadió HCl 2,0 M en éter dietílico (210 g, 281 ml, 1,02 equiv.) durante 15-20 minutos. Después de la adición de HCl, se observó una suspensión de color blanco. Se agitó a temperatura ambiente durante aproximadamente 16-20 horas. El producto se recogió por filtración y se aclaró con acetato de etilo (2 x 500 ml cada uno). La torta húmeda se secó a 50-55°C/<5 mm de Hg durante 16-20 horas hasta alcanzar un peso constante. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida, monohidrocloruro, (245,9 g, 544,7 mmol, rendimiento de 96%) en forma de un sólido de color blanco. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,32 (d, J = 6,57 Hz, 6 H) 2,18 (s, 3 H) 3,70 (s, 3 H) 4,35-4,62 (m, 1 H) 6,12 (s a, (s a, 1 H) 6,60 (s a, (s a, 1 H) 7,19-7,41 (m, 1 H) 7,48-7,75 (m, 3 H) 8,09 (s, 1 H) 9,59-9,99 (m, 2 H) 11,98 (s a, (s a, 1 H). HPLC C18 Tr = 6,1 minutos (pureza de 99,6%). MS (ESI): 414,8 [M+H]⁺.

Ejemplo 42

20 2-[(5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-etilbenzamida

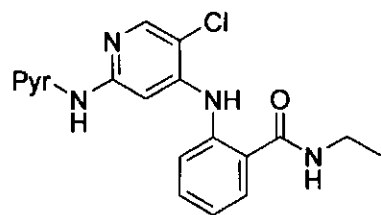


Un recipiente se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-etilbenzamida (100 mg, 0,322 mmol), 1-etil-3-metil-1H-pirazol-5-amina (60,5 mg, 0,484 mmol), carbonato de cesio (315 mg, 0,967 mmol), 1,4-dioxano (5,0 ml) y THF (1,0 ml). La

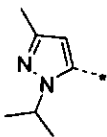
mezcla de reacción se desgasificó por nitrógeno durante 10 min, momento en el que se añadieron (±)-2,2'-bis(difenilfosfino)-1,1'-binaftaleno (40,1 mg, 0,064 mmol) y acetato de paladio (II) (7,24 mg, 0,032 mmol) en una cantidad mínima de 1,4-dioxano. El recipiente se cerró herméticamente y la mezcla de reacción se calentó en un horno de microondas a 160°C durante 40 min. La suspensión resultante se enfrió a temperatura ambiente y se filtró a través de celite. El filtrado se evaporó a sequedad y la mezcla de reacción en bruto se purificó por HPLC de fase inversa para dar el compuesto del título en forma de un sólido (45 mg, rendimiento de 30%); MS: M(C₂₀H₂₃ClN₆O) = 398,89, (M+H)⁺ = 399, 401; 1H RMN (400 MHz, CLOROFORMO-d) δ ppm 8,34 (s, 1 H) 7,94 (s, 1 H) 7,66 (s a, 1 H) 7,51 (d, J = 7,8 Hz, 1 H) 7,31 - 7,47 (m, 2 H) 6,96 - 7,17 (m, 1 H) 6,58 (s, 1 H) 6,19 (t, J = 5,2 Hz, 1 H) 5,86 (s, 1H) 4,01 (c, J = 7,3 Hz, 2 H) 3,42 - 3,62 (m, 2 H) 2,24 (s, 3 H) 1,37 (t, J = 7,3 Hz, 3 H) 1,26 (t, J = 7,3 Hz, 3 H).

Los compuestos de 2-({5-cloro-2-(1H-pirazol-5-il)amino}-4-piridinil)amino)-N-etilbenzamida ilustrados en la Tabla 5 se prepararon a partir de 2-[(2,5-dicloro-4-piridinil)amino]-N-etilbenzamida y amino-pirazoles sustancialmente de acuerdo con el procedimiento del Ejemplo 42.

Tabla 5

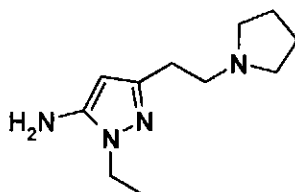


Ex	Nombre	Pir	Datos
43	2-({5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-etilbenzamida		LC-MS (ES) m/z = 385 (M+H) ⁺ ; 1H RMN (400 MHz, MeOD) δ ppm 7,91 (s, 1 H) 7,67 (dd, J = 7,8, 1,52 Hz, 1 H) 7,44 - 7,58 (m, 2 H) 7,14 -7,24 (m, 1 H) 6,61 (s, 1 H) 5,98 (s, 1 H) 3,62 (s, 3 H) 3,37 - 3,46 (m, 2 H) 2,19 (s, 3 H) 1,21 (t, J = 7,3 Hz, 3H)
44	2-({5-Cloro-2-[(1-etil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-etilbenzamida		LC-MS (ES) m/z = 415, 416 (M+H) ⁺ ; 1H RMN (400 MHz, CLOROFORMO-d) δ ppm 9,85 (s, 1 H) 8,00 (s, 1 H) 7,46 - 7,54 (m, 2 H)

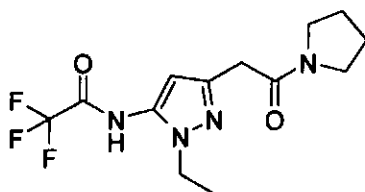
Ex	Nombre	Pir	Datos
			7,33 - 7,44 (m, 2 H) 6,88 - 7,12 (m, 1 H) 6,72 (s a, 1 H) 6,52 (s, 1 H) 5,93 - 6,17 (m, 2 H) 4,09 (c, J = 7,2 Hz, 2 H) 3,38 - 3,57 (m, 2 H) 1,34 - 1,49 (m, 3 H) 1,26 (t, J = 7,3 Hz, 3 H)
45	2-[(5-Cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-etilbenzamida		LC-MS (ES) m/z = 413 (M+H) ⁺ ; 1H RMN (400 MHz, DMSO-d ₆) δ ppm 10,04 (s, 1 H) 8,71 (t, J = 5,4 Hz, 1 H) 8,48 (s, 1 H) 7,97 (s, 1 H) 7,71 (dd, J = 7,8, 1,26 Hz, 1 H) 7,44 - 7,59 (m, 2 H) 7,04 - 7,19 (m, 1 H) 6,69 (s, 1 H) 5,93 (s, 1 H) 4,30 - 4,45 (m, 1H) 3,22 - 3,31 (m, 2 H) 2,10 (s, 3 H) 1,29 - 1,36 (d, J = 8,0 Hz 6 H) 1,12 (t, J = 7,2 Hz, 3 H)

Intermedio 6

1-Etil-3-[2-(1-pirrolidinil)etil]-1H-pirazol-5-amina



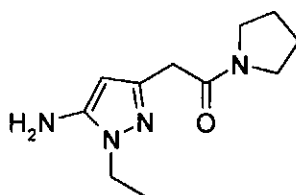
5 Int. 6a) N-[1-Etil-3-[2-oxo-2-(1-pirrolidinil)etil]-1H-pirazol-5-il]-2,2,2-trifluoroacetamida



10 Se añadió gota a gota trifluoroacetato de pentafluorofenilo (497 mg, 1,773 mmol) a una solución en agitación de ácido acético (5-amino-1-etil-1H-pirazol-3-ilo) (150 mg, 0,887 mmol) y piridina (0,143 ml, 1,773 mmol) en DMF (3 ml). La mezcla de reacción se agitó durante 15 min y se añadió pirrolidina (0,220 ml, 2,66 mmol). La mezcla de reacción se agitó a 65°C durante 40 min. La mezcla se enfrió, se

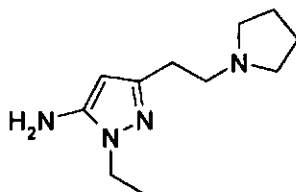
inactivó con agua (5 ml) y se extrajo con EtOAc (3 x). El extracto se secó sobre Na_2SO_4 , se filtró y se concentró. El residuo se purificó usando RP-HPLC para dar el producto (125 mg). MS: $(\text{M}+\text{H})^+ = 318,8$. ^1H RMN (400 MHz, $\text{CLOROFORMO-}d$) δ ppm 1,32 (t, $J = 7,2$ Hz, 3H), 1,87 - 2,06 (m, 4 H), 3,46 (t, $J = 6,8$ Hz, 2H), 3,53 (t, $J = 6,8$ Hz, 2H), 3,66 (s, 2H), 4,07 (c, $J = 7,2$ Hz, 2H), 5,30 (s, 1H).

Int. 6b) 1-etil-3-[2-oxo-2-(1-pirrolidinil)etil]-1H-pirazol-5-amina



A una solución de N-{1-etil-3-[2-oxo-2-(1-pirrolidinil)etil]-1H-pirazol-5-il}-2,2,2-trifluoroacetamida (120 mg, 0,377 mmol) en metanol (1,5 ml) se le añadió HCl 2 M (1 ml, 0,377 mmol) y la mezcla de reacción se agitó a 50°C durante 2 h y se concentró. El residuo se neutralizó usando una solución saturada de NaHCO_3 y se concentró. El residuo se secó a alto vacío para dar 79 mg y se usó para la siguiente reacción sin purificación adicional. MS: $(\text{M}+\text{H})^+ = 222,8$. ^1H RMN (400 MHz, $\text{DMSO-}d_6$) δ ppm 1,18 (t, $J = 7,2$ Hz, 3H), 1,70 - 1,85 (m, 4 H), 3,24 (t, $J = 6,8$ Hz, 2H), 3,31 (s, 2 H), 3,43 (t, $J = 6,8$ Hz, 2H), 3,78 (c, $J = 7,2$ Hz, 2H), 5,11 (s, 1H).

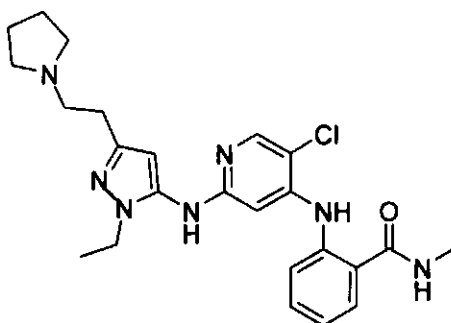
Int. 6c) 1-etil-3-[2-(1-pirrolidinil)etil]-1H-pirazol-5-amina



A una solución de 1-etil-3-[2-oxo-2-(1-pirrolidinil)etil]-1H-pirazol-5-amina (600 mg, 1,784 mmol) en tetrahidrofurano (8 ml) enfriada con un baño de agua enfriada con hielo se le añadió gota a gota una solución de LAH 2 M (1,0 ml, 2,00 mmol) y la mezcla de reacción se agitó durante 5 h a ta y durante 30 min a 50°C. La mezcla de reacción se inactivo cuidadosamente con metanol seguido de agua y concentró. El residuo se lavó 5 veces con DCM/metanol. El extracto se concentró y el residuo se purificó usando HPLC en condiciones básicas para dar 220 mg de producto. MS: $(\text{M}+\text{H})^+ = 208,7$. ^1H RMN (400 MHz, $\text{CLOROFORMO-}d$) δ ppm 1,37 (t, $J = 7,2$ Hz, 3H), 1,79 (m, 4H), 2,56 (m, 4H), 2,71 (m, 2H), 3,42 (m, 2H), 3,94 (c, $J = 7,2$ Hz, 2H), 5,40 (s, 1H).

Ejemplo 46

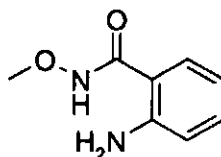
2-[[5-Cloro-2-({1-etil-3-[2-(1-pirrolidinil)etil]-1H-pirazol-5-il}amino)-4-piridinil]amino]-N-metilbenzamida



A un tubo para microondas de 5 ml se le añadieron 2-[[2,5-dicloro-4-
5 piridinil]amino]-N-metilbenzamida (100 mg, 0,338 mmol), 1-etil-3-[2-(1-
pirrolidinil)etil]-1H-pirazol-5-amina (70,3 mg, 0,338 mmol), carbonato de cesio (330
mg, 1,013 mmol) y 1,4-dioxano (2 ml), y la mezcla se desgasificó por burbujeo de
nitrógeno durante 15 min. Se añadieron acetato de paladio (II) (3,79 mg, 0,017
mmol) y BINAP (21,03 mg, 0,034 mmol) y la mezcla de reacción se calentó a 170°C
10 con agitación en condiciones de microondas durante 40 min. La mezcla de reacción
se filtró y se concentró. El residuo se purificó usando RP-HPLC en condiciones
básicas (Gemini 5u C18(2) 110A, AXI. 50 x 30,00 mm 5 micrómetros: realización de
7,3 minutos, 47 ml/min, ACN al 40%/H₂O, de NH₄OH al 0,1% a ACN al 90%/H₂O,
NH₄OH al 0,1% con detección UV a 254 nm) para dar el compuesto del título (62
15 mg). MS: (M+H)⁺ = 468,1. ¹H RMN (400 MHz, DMSO-d₆) δ ppm 1,21 (t, J = 7,2 Hz, 3
H), 1,67 (m, 4H), 2,45 (m, 4), 2,60 (m, 4H), 2,77 (d, J = 4,0 Hz, 3H), 3,89 (c, J = 7,2
Hz, 2H), 6,03 (s, 1H), 6,74 (s, 1H), 7,11 (m, 1H), 7,49 (m, 1H), 7,54 (m, 1H), 7,71 (d,
J = 7,2 Hz, 1H), 8,00 (s, 1H).

Intermedio 7

2-Amino-N-metoxi-benzamida

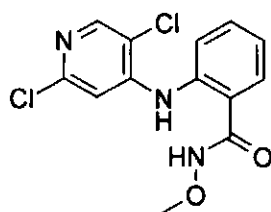


A una mezcla de anhídrido isatoico (40 g, 245,39 mmol, 1 equiv.) y
hidrocloruro de o-metil hidroxilamina (30,55 g, 368,09 mmol, 1,5 equiv.) en
EtOH:H₂O (9:1) (1000 ml) se le añadió trietilamina (51,2 ml, 368,09 mmol, 1,5
25 equiv.) y la mezcla resultante se calentó a reflujo durante 4 h. Después de que se
completara la reacción, el disolvente se retiró a presión reducida y el residuo se

diluyó con agua (500 ml) y se extrajo con acetato de etilo (3 x 250 ml). La capa orgánica combinada se secó sobre sulfato sódico, se filtró y se concentró a presión reducida. El compuesto sólido obtenido de este modo se purificó por lavado con éter dietílico y hexano para dar el compuesto del título en forma de un sólido de color pardo (20 g, 49%). ¹H RMN (400 MHz, DMSO-*d*₆): δ 3,67 (s, 3H), 6,20-6,40 (s a, 2H), 6,44-6,53 (m, 1H), 6,70 (d, 1H, *J* = 7,76 Hz), 7,10-7,19 (m, 1H), 7,30 (d, 1H, *J* = 7,6 Hz), 11,40 (s, 1H). LC-MS [*M* + *H*]⁺ = 167,2.

Intermedio 8

2-(2,5-Dicloropiridin-4-il-amino)-*N*-metoxi-benzamida (CR637-KS210635-027A1)



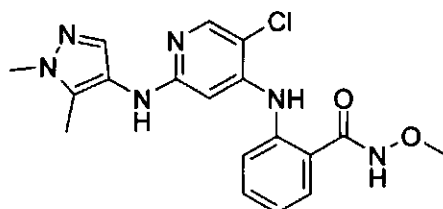
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Una mezcla de 2,5-dicloro-4-yodo-piridina (40 g, 146,5 mmol, 1 equiv.), 2-amino-*N*-metoxi-benzamida (24,32 g, 146,5 mmol, 1 equiv.) y K₃PO₄ (77,72 g 366,2 mmol, 2,5 equiv.) en 1,4-dioxano (600 ml) se desgasificó con N₂ durante 1 h. A esto se le añadieron Pd(OAc)₂ (0,657 g, 2,93 mmol, 0,02 equiv.) y DPEPhos (6,31 g, 11,7 mmol, 0,08 equiv.) y se desgasificó de nuevo durante 15 min con N₂. La mezcla resultante se agitó a 110°C durante una noche. Después de que se completara la reacción, el material sólido se recogió por filtración, se disolvió en agua (500 ml) y se extrajo con acetato de etilo (5 x 200 ml). La capa orgánica combinada se secó sobre sulfato sódico, se filtró y se concentró a presión reducida. El compuesto sólido obtenido de este modo se purificó por lavado con hexano para dar el compuesto del título en forma de un sólido de color amarillento (40 g, 53%). ¹H RMN (400 MHz, DMSO-*d*₆): δ 3,63 (s, 3H), 7,06 (s, 1H), 7,15-7,22 (m, 1H), 7,48-7,57 (m, 2H), 7,66-7,67 (d, 1H, *J* = 7,48 Hz), 8,25 (s, 1H), 10,66-11,45 (s a, 1H). LC-MS [*M* + *H*]⁺ = 312,3.

25

Ejemplo 47

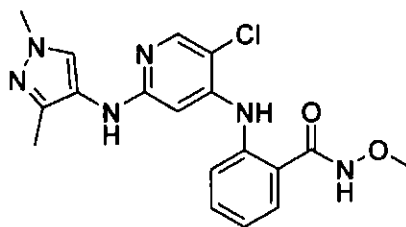
2-({5-Cloro-2-[(1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida



Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (200 mg, 0,64 mmol), 1,5-dimetil-1H-pirazol-4-amina (142 mg, 1,28 mmol), carbonato de cesio (626 mg, 1,92 mmol) y dioxano/THF (3:1 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (5,8 mg, 0,03 mmol) y BINAP (40 mg, 0,06 mmol). El tubo se cerró herméticamente y la mezcla se agitó en un baño de aceite a 150°C durante una noche. La solución de color pardo oscuro se filtró a través de celite y se evaporó. Se disolvió en MeOH, se filtró a través de un Acrodisc (Pall Corporation; www.pall.com) y se purificó adicionalmente por HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). El residuo oleoso de color pardo oscuro se disolvió en DMF y se añadió lentamente agua. Se formó un precipitado de color castaño, se retiró por filtración y se secó al vacío a 40°C durante 2 h para producir el producto deseado (18 mg, 7,3%) en forma de un sólido de color castaño. LC-MS [M+H]⁺ = 387,1, 389,1. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 11,91 (s a, 1 H) 9,41 (s a, 1 H) 7,85 - 7,98 (m, 2 H) 7,49 - 7,59 (m, 3 H) 7,42 (s a, 1 H) 7,07 - 7,13 (m, 1 H) 6,50 (s a, 1 H) 3,69 (d, J = 10,36 Hz, 6 H) 2,11 (s, 3 H).

Ejemplo 48

2-[(5-Cloro-2-[(1,3-dimetil-1H-pirazol-4-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida



20

Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (250 mg, 0,8 mmol), 1,3-dimetil-1H-pirazol-4-amina (187 mg, 1,68 mmol), carbonato de cesio (783 mg, 2,4 mmol) y dioxano/THF (3:1 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (9 mg, 0,04 mmol) y BINAP (50 mg, 0,08 mmol). La mezcla se agitó en un microondas a 140°C durante 40 min. Se evaporó y el residuo se disolvió en MeOH, se filtró a través de celite, a través de un Acrodisc y se purificó adicionalmente usando HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). Las fracciones se combinaron y se evaporaron. Se añadió éter al residuo y se formó un precipitado de color castaño. Se retiró por filtración y se secó al vacío a 40°C durante 2 días para producir el

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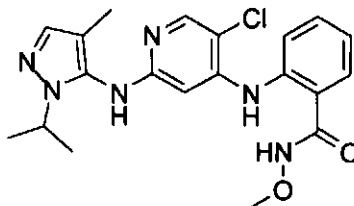
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producto deseado (55 mg, 18%) en forma de un sólido de color castaño. LC-MS (ES) $m/z = 387,1$, $[M+H]^+ = 389,1$, ^1H RMN (400 MHz, DMSO- d_6) δ ppm 11,93 (s a, 1 H) 9,51 (s a, 1 H) 8,03 (s, 1 H) 7,96 (s, 1 H) 7,82 (s, 1 H) 7,51 - 7,61 (m, 3 H) 7,07 - 7,15 (m, 1 H) 6,68 (s, 1 H) 3,70 (d, $J = 4,29$ Hz, 6 H) 2,07 (s, 3 H).

5

Ejemplo 49

2-[(5-Cloro-2-[(4-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida

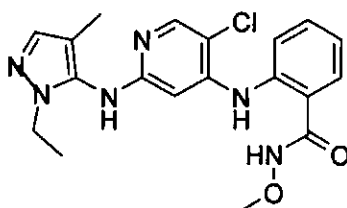


Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (100 mg, 0,32 mmol), 4-metil-1-(1-metiletil)-1H-pirazol-5-amina (93,6 mg, 0,67 mmol), carbonato de cesio (312,8 mg, 0,96 mmol) y DMF (5 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (3,6 mg, 0,016 mmol) y BINAP (19,9 mg, 0,032 mmol). La mezcla de reacción se calentó en un baño de aceite durante 6 horas y después en un microondas a 150°C durante 40 min. El disolvente se evaporó y el residuo se disolvió en MeOH. Se filtró a través de celite y a través de un Acrodisc para purificarse por HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). Las fracciones se combinaron y se evaporaron. El residuo oleoso de color pardo se diluyó en DMF y se añadió agua. Se formó un precipitado. Se filtró y se secó al vacío a 40°C durante 6 h. LC-MS $[M+H]^+ = 415,1$. ^1H RMN (400 MHz, DMSO- d_6) δ ppm 11,93 (s, 1 H) 9,48 (s a, 1 H) 8,23 (s, 1 H) 7,93 (s, 1 H) 7,58 (d, $J = 7,83$ Hz, 1 H) 7,50 (d, $J = 3,79$ Hz, 2 H) 7,24 (s, 1 H) 7,12 (dt, $J = 7,83$, 4,17 Hz, 1 H) 6,40 (s a, 1 H) 4,33 (dt, $J = 13,14$, 6,57 Hz, 1 H) 3,71 (s, 3 H) 1,78 (s, 3 H) 1,26 (d, $J = 6,57$ Hz, 6 H).

25

Ejemplo 50

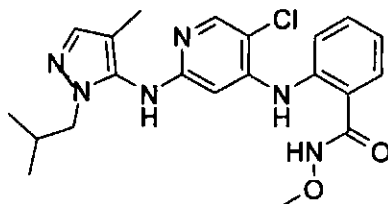
2-[(5-Cloro-2-[(1-etil-4-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida



Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (300 mg, 0,96 mmol), 1-etil-4-metil-1H-pirazol-5-amina (253 mg, 2,01 mmol), carbonato de cesio (939 mg, 2,88 mmol) y DMF (7 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (10,8 mg, 0,05 mmol) y BINAP (59,8 mg, 0,096 mmol). La mezcla de reacción se calentó en un baño de aceite a 90°C durante 5 h y después en un microondas a 150°C durante 50 min. Se evaporó y el residuo se disolvió en MeOH, se filtró a través de celite y a través de un Acrodisc y se purificó adicionalmente por HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). Las fracciones se combinaron y se evaporaron. El residuo oleoso de color pardo se diluyó en DMF y se añadió agua. Se formó un precipitado. Se retiró por filtración y se secó al vacío a 40°C durante 5 h. LC-MS $[M+H]^+ = 401,1$. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 11,92 (s, 1 H) 9,48 (s a, 1 H) 8,27 (s, 1 H) 7,94 (s, 1 H) 7,59 (d, J = 7,58 Hz, 1 H) 7,51 (d, J = 3,54 Hz, 2 H) 7,22 (s, 1 H) 7,09 - 7,16 (m, 1 H) 6,40 (s, 1 H) 3,85 (c, J = 7,33 Hz, 2 H) 3,71 (s, 3 H) 1,79 (s, 3 H) 1,21 (t, J = 7,20 Hz, 3 H).

Ejemplo 51

2-[(5-Cloro-2-[(4-metil-1-(2-metiletilpropilpropil)propil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida

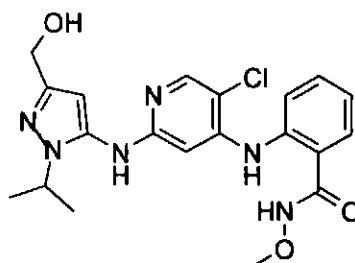


Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (300 mg, 0,96 mmol), 4-metil-1-(2-metiletilpropilpropilpropil)-1H-pirazol-5-amina (309 mg, 2,01 mmol), carbonato de cesio (939 mg, 2,88 mmol) y DMF (5 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (10,8 mg, 0,05 mmol) y BINAP (59,8 mg, 0,096 mmol). La mezcla de reacción se calentó en un baño de aceite a

90°C durante 5 h y después en un microondas a 150°C durante 40 min. El disolvente se evaporó y el residuo se disolvió en MeOH, se filtró a través de celite y a través de un Acrodisc y se purificó adicionalmente usando HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). Las fracciones se combinaron y se evaporaron. El residuo oleoso de color pardo se diluyó en DMF y se añadió agua. Se formó un precipitado. Se retiró por filtración y se secó al vacío a 40°C durante 5 h. LC-MS $[M+H]^+ = 429,1$. ^1H RMN (400 MHz, DMSO- d_6) δ ppm 11,93 (s, 1 H) 9,48 (s a, 1 H) 8,26 (s, 1 H) 7,94 (s, 1 H) 7,58 (d, $J = 7,33$ Hz, 1 H) 7,44 - 7,51 (m, 2 H) 7,23 (s, 1 H) 7,08 - 7,16 (m, 1 H) 6,38 (s, 1 H) 3,70 (s, 3 H) 3,65 (d, $J = 7,33$ Hz, 2 H) 2,03 (dt, $J = 13,71, 6,92$ Hz, 1 H) 1,77 (s, 3 H) 0,75 (d, $J = 6,57$ Hz, 6 H).

Ejemplo 52

2-[(5-Cloro-2-[[3-(hidroximetil)-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida



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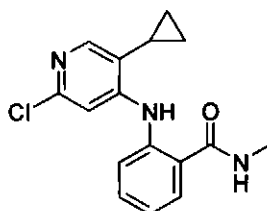
Un tubo para microondas se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-N-(metiloxi)benzamida (188 mg, 0,602 mmol), [5-amino-1-(1-metiletil)-1H-pirazol-3-il]metanol (140 mg, 0,90 mmol), carbonato de cesio (589 mg, 1,81 mmol) y DMF (5 ml). La mezcla de reacción se desgasificó en una atmósfera de nitrógeno durante 10 min y se añadieron acetato de paladio (II) (6,8 mg, 0,03 mmol) y BINAP (37,5 mg, 0,06 mmol). La mezcla de reacción se calentó en un baño de aceite a 90°C durante 5 h y después en un microondas a 150°C durante 40 min. Se evaporó y el residuo se disolvió en MeOH, se filtró a través de celite y a través de un Acrodisc y se purificó adicionalmente usando HPLC preparativa Agilent (agua de 5 a 95%:acetonitrilo con ácido fórmico al 0,1%). Las fracciones se combinaron y se evaporaron. Al residuo oleoso de color pardo se le añadió EtOAc. Después, la mezcla se calentó y se añadió gota a gota hexano. Se formó un precipitado de color amarillo claro tras la sonicación. Se retiró por filtración y se secó al vacío a 40°C durante 12 h. LC-MS $[M+H]^+ = 431,2$. ^1H RMN (400 MHz, DMSO- d_6) δ ppm 11,93 (s a, 1 H) 9,54 (s a, 1 H) 8,54 (s, 1 H) 7,96 - 8,01 (m, 1 H) 7,52 - 7,62 (m, 3 H) 7,11 -

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7,16 (m, 1 H) 6,70 (s, 1 H) 6,10 (s, 1 H) 4,95 (t, $J = 5,81$ Hz, 1 H) 4,43 (dt, $J = 13,14$, 6,57 Hz, 1 H) 4,33 (d, $J = 5,56$ Hz, 2 H) 3,71 (s, 3 H) 1,29 (d, $J = 6,57$ Hz, 6 H).

Intermedio 9

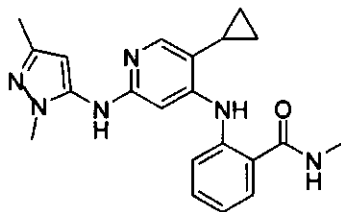
2-(2-Cloro-5-ciclopropil-piridin-4-il-amino)-*N*-metil-benzamida 1



5 Una solución de ácido ciclopropilborónico (0,38 g, 4,40 mmol, 1,5 equiv.) en tolueno (100 ml) se desgasificó con N_2 a 50°C durante 15 min. A esto se le añadieron $Pd(PPh_3)_4$ (0,17 g, 0,15 mmol, 0,05 equiv.) y 2-(5-bromo-2-cloro-piridin-4-il-amino)-*N*-metil-benzamida (1 g, 2,93 mmol, 1 equiv.) y la mezcla de reacción
10 resultante se desgasificó de nuevo durante 30 min. A esta solución desgasificada se le añadió en una porción K_3PO_4 (2,49 g, 11,72 mmol, 4 equiv.) en H_2O (4 ml) y la mezcla de reacción resultante se calentó a reflujo durante una noche. El disolvente se retiró a presión reducida, el residuo se diluyó con agua (100 ml) y después se extrajo con DCM (3 x 75 ml). La capa orgánica combinada se secó sobre sulfato
15 sódico, se filtró y se concentró a presión reducida para producir el producto en bruto. El compuesto en bruto se purificó por cromatografía en columna sobre gel de sílice (malla 60-120) usando MeOH al 50%-DCM como eluyente para dar el compuesto del título en forma de un sólido de color amarillo pálido (0,480 g, 54%).
20 ^1H RMN (400 MHz, $DMSO-d_6$): δ 0,60-0,70 (m, 2H), 0,95-1,05 (m, 2H), 1,60-1,71 (m, 1H), 2,76 (d, 3H, $J = 4,48$ Hz), 7,09 (s, 1H), 7,10-7,18 (m, 1H), 7,49-7,60 (m, 2H), 7,68-7,70 (d, 1H, $J = 7,64$ Hz), 7,93 (s, 1H), 8,60-8,70 (m, 1H), 10,22 (s, 1H).
LC-MS $[M+H]^+ = 302,0$.

Ejemplo 53

2-[5-Ciclopropil-2-(2,5-dimetil-2*H*-pirazol-3-il-amino)-piridin-4-il-amino]-*N*-metil-benzamida

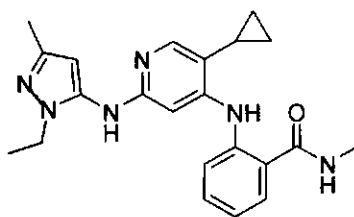


A un tubo para microondas de 10 ml se le añadieron 2-(2-cloro-5-ciclopropil-

piridin-4-il-amino)-*N*-metil-benzamida (0,075 g, 0,25 mmol, 1 equiv.), 2,5-dimetil-2*H*-pirazol-3-il-amina (0,030 g, 0,27 mmol, 1,1 equiv.), Cs₂CO₃ (0,23 g, 0,70 mmol, 2,8 equiv.) y 1,4-dioxano (4 ml) y la mezcla resultante se desgasificó con N₂ durante 30 minutos. A esto se le añadieron Pd₂(dba)₃ (0,008 g, 0,007 mmol, 0,03 equiv.) y xanthphos (0,009 g, 0,014 mmol, 0,06 equiv.) y la mezcla de reacción se desgasificó de nuevo con N₂ durante 15 minutos más. La mezcla de reacción resultante se irradió en un microondas CEM a 110°C y a 150 W durante 40 min. El progreso de la reacción se controló por LCMS. Después de que se completara la reacción, el Cs₂CO₃ se retiró por filtración y el filtrado se concentró a presión reducida para dar un producto en bruto. El compuesto en bruto se purificó por cromatografía en columna sobre alúmina neutra usando MeOH al 0,1%-DCM como eluyente. El compuesto sólido obtenido de este modo se lavó con éter dietílico y pentano para dar el compuesto del título en forma de un sólido de color amarillento (16 mg, 17%). ¹H RMN (400 MHz, DMSO-*d*₆): δ 0,52-0,59 (m, 2H), 0,89-0,99 (m, 2H), 1,52-1,62 (m, 1H), 2,05 (s, 3H), 2,76-2,77 (d, 3H, *J* = 4,44 Hz), 3,52 (s, 3H), 5,96 (s, 1H), 6,69 (s, 1H), 7,01-7,05 (t, 1H, *J* = 7,48 Hz), 7,42-7,45 (m, 1H), 7,51-7,60 (m, 1H) 7,64-7,66 (d, 1H, *J* = 7,32 Hz), 7,72 (s, 1H), 8,37 (s, 1H), 8,55-8,65 (s a, 1H), 9,96 (s, 1H). LC-MS [M+H]⁺ = 377,2.

Ejemplo 54

20 2-[5-Ciclopropil-2-(2-etil-5-metil-2*H*-pirazol-3-il-amino)-piridin-4-il-amino]-*N*-metilbenzamida

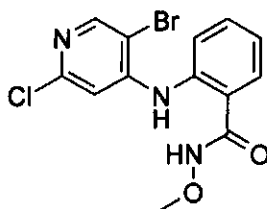


A un tubo para microondas de 10 ml se le añadieron 2-(2-cloro-5-ciclopropil-piridin-4-il-amino)-*N*-metil-benzamida (0,075 g, 0,25 mmol, 1 equiv.), 2-etil-5-metil-2*H*-pirazol-3-il-amina (0,035 g, 0,27 mmol, 1,1 equiv.), Cs₂CO₃ (0,23 g, 0,70 mmol, 2,8 equiv.) y 1,4-dioxano (3 ml) y la mezcla resultante se desgasificó con N₂ durante 30 minutos. A esta mezcla se le añadieron Pd₂(dba)₃ (0,008 g, 0,007 mmol, 0,03 equiv.) y xanthphos (0,009 g, 0,015 mmol, 0,06 equiv.) y esta mezcla se desgasificó de nuevo con N₂ durante 10 minutos más. La mezcla de reacción resultante se irradió en un microondas CEM a 110°C y a 150 W durante 45 min. El progreso de la reacción se controló por LCMS. Después de que se completara la reacción, el

Cs₂CO₃ se retiró por filtración y el filtrado se concentró a presión reducida para dar un producto en bruto. Se purificó usando cromatografía en columna sobre alúmina neutra usando MeOH al 0,2%-DCM como eluyente. El compuesto sólido obtenido de este modo se lavó con éter dietílico y hexano para dar el compuesto del título en forma de un sólido de color blanco (20 mg, 20%). ¹H RMN (400 MHz, DMSO-*d*₆): δ 0,50-0,62 (m, 2H), 0,88-0,99 (m, 2H), 1,15-1,28 (m, 3 H), 1,55-1,65 (m, 1H), 2,07 (s, 3H), 2,76-2,77 (d, 3H, *J* = 4,36 Hz), 3,82-3,95 (m, 2H), 5,95 (s, 1H), 6,68 (s, 1H), 6,99-7,10 (m, 1H), 7,42-7,50 (m, 1H), 7,50-7,55 (m, 1H) 7,64-7,66 (d, 1H, *J* = 7,6 Hz), 7,71 (s, 1H), 8,30 (s, 1H), 8,55-8,70 (s a, 1H), 9,95 (s, 1H). LC-MS [M+H]⁺ = 391,4.

Intermedio 10

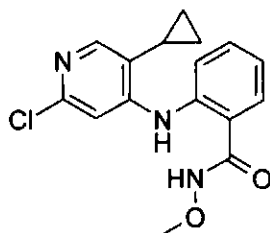
2-(5-Bromo-2-cloro-piridin-4-il-amino)-*N*-metoxi-benzamida



Una mezcla de 5-bromo-2-cloro-4-yodo-piridina (5 g, 15,72 mmol, 1 equiv.), 2-amino-*N*-metoxi-benzamida (2,61 g, 15,72 mmol, 1 equiv.), K₃PO₄ (8,34 g, 39,3 mmol, 2,5 equiv.) y 1,4-dioxano (30 ml) se desgasificó con N₂ durante 1 h. A esto se le añadieron DPEPhos (0,67 g, 1,25 mmol, 0,08 equiv.) y Pd(OAc)₂ (0,07 g, 0,31 mmol, 0,02 equiv.) y esta mezcla se desgasificó de nuevo con N₂ durante 30 min. La mezcla resultante se calentó a reflujo durante una noche. Después de que se completara la reacción, el disolvente se retiró a presión reducida y el residuo se diluyó con agua (100 ml) y se extrajo con MeOH al 5%-DCM (3 x 100 ml). Las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida para dar un compuesto en bruto. Se purificó por cromatografía en columna sobre gel de sílice (malla 60-120) usando acetato de etilo al 20%-hexano como eluyente para producir el compuesto del título en forma de un sólido de color blanquecino (3,5 g, 62%). ¹H RMN (400 MHz, DMSO-*d*₆): δ 3,56 (s, 3H), 6,88-6,98 (m, 1H), 7,08 (s, 1H), 7,17-7,25 (m, 1H), 7,26-7,35 (m, 1H), 7,82-7,90 (m, 1H), 8,23 (s, 1H), 12,86 (s a, 1H). LC-MS [M+H]⁺ = 356,30.

Intermedio 11

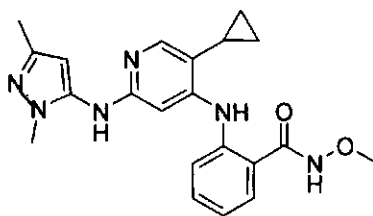
2-(2-Cloro-5-ciclopropil-piridin-4-il-amino)-*N*-metoxi-benzamida



En un tubo que puede cerrarse herméticamente se desgasificó tolueno (50 ml) con N₂ a 50°C durante 15 min, a esto se le añadieron 2-(5-bromo-2-cloro-piridin-4-ilamino)-*N*-metoxi-benzamida (1,5 g, 4,21 mmol, 1 equiv.), ácido ciclopropilborónico (1,4 g, 16,85 mmol, 4 equiv.) y Pd(PPh₃)₄ (0,24 g, 0,21 mmol, 0,05 equiv.) y la mezcla resultante se desgasificó durante 30 min. A esto se le añadieron NaBr (0,44 g, 4,33 mmol, 1,03 equiv.) y una solución de KF (0,8 g, 13,90 mmol, 3,3 equiv.) en H₂O (3 ml); y se desgasificó de nuevo con N₂ durante 15 min. El tubo se cerró herméticamente y la mezcla resultante se calentó a 100°C durante 24 h. Después de que se completara la reacción, la mezcla de reacción se dejó enfriar a temperatura ambiente, se vertió en agua (100 ml) y se extrajo con tolueno (2 x 50 ml). La capa orgánica combinada se secó sobre sulfato sódico, se filtró y se concentró a presión reducida. El compuesto en bruto se purificó por lavado con DCM al 0,5%-Et₂O para dar el compuesto del título en forma de un sólido de color amarillo pálido (0,7 g, 53%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 0,57-0,72 (m, 2H), 0,97-1,10 (m, 2H), 1,62-1,75 (m, 1H), 3,68 (s, 3H), 7,02 (s, 1H), 7,11-7,20 (m, 1H), 7,51-7,67 (m, 3H), 7,94 (s, 1H), 9,62 (s, 1H), 11,92 (s a, 1H). LC-MS [M+H]⁺ = 318,2.

Ejemplo 55

2-[5-Ciclopropil-2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-piridin-4-ilamino]-*N*-metoxi-benzamida

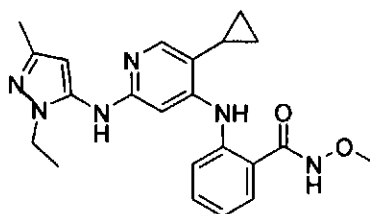


A un tubo para microondas de 10 ml se le añadieron 2-(2-cloro-5-ciclopropil-piridin-4-ilamino)-*N*-metoxi-benzamida (0,075 g, 0,24 mmol, 1 equiv.), 2,5-dimetil-2*H*-pirazol-3-ilamina (0,05 g, 0,47 mmol, 2 equiv.), Cs₂CO₃ (0,23 g, 0,71 mmol, 3 equiv.) y 1,4-dioxano (3 ml). La mezcla resultante se desgasificó con N₂ durante 15 min. A esto se le añadieron Pd₂(dba)₃ (0,015 g, 0,014 mmol, 0,06 equiv.) y

xanthphos (0,03 g, 0,06 mmol, 0,25 equiv.) y la mezcla se desgasificó de nuevo con N₂ durante 30 min. La mezcla resultante se irradió en un microondas CEM a 120°C, a 150 W durante 35 min. Después de que se completara la reacción, el disolvente se retiró a presión reducida y el compuesto en bruto se purificó usando
5 cromatografía en columna sobre gel de sílice (malla 100-200) usando MeOH al 1%-DCM como eluyente seguido de HPLC prep. El compuesto sólido obtenido de esta manera se lavó con éter dietílico y pentano para dar el compuesto del título en forma de un sólido de color blanquecino (11 mg, 12%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 0,52-0,60(m, 2H), 0,82-1,00 (m, 2H), 1,50-1,62 (m, 1H), 2,05 (s, 3H), 3,52 (s,
10 3H), 3,70 (s, 3H), 5,96 (s, 1H), 6,67 (s, 1H), 6,98-7,10 (m, 1H), 7,40-7,60 (m, 3H), 7,73 (s, 1H), 8,39 (s, 1H), 9,46 (s, 1H), 11,88 (s a, 1H). LC-MS [M+H]⁺ = 393,4.

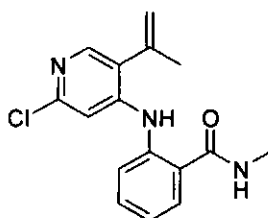
Ejemplo 56

2-[5-Ciclopropil-2-(2-etil-5-metil-2H-pirazol-3-ilamino)-piridin-4-ilamino]-N-metoxi-benzamida



15

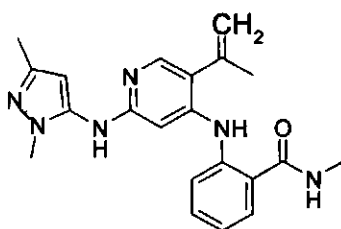
A un tubo para microondas de 10 ml se le añadieron 2-(2-cloro-5-ciclopropil-piridin-4-ilamino)-N-metoxi-benzamida (0,075 g, 0,24 mmol, 1 equiv.), 2-etil-5-metil-2H-pirazol-3-ilamina (0,05 g, 0,36 mmol, 1,5 equiv.), Cs₂CO₃ (0,23 g, 0,71 mmol, 3 equiv.) y 1,4-dioxano (3 ml) y la mezcla resultante se desgasificó con N₂ durante 15
20 min. A esto se le añadieron Pd₂(dba)₃ (0,014 g, 0,014 mmol, 0,06 equiv.) y xanthphos (0,03 g, 0,06 mmol, 0,25 equiv.) y esta mezcla se desgasificó de nuevo con N₂ durante 10 min más. La mezcla resultante se irradió en un microondas CEM a 120°C, a 150 W durante 35 min. Después de que finalizara la reacción, el disolvente se retiró a presión reducida y el producto en bruto se purificó por
25 cromatografía en columna sobre gel de sílice (malla 100-200) usando MeOH al 1%-DCM como eluyente seguido de lavado con éter dietílico y pentano y DCM para dar el compuesto del título en forma de un sólido de color blanquecino (5 mg, 5%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 0,50-0,60 (m, 2H), 0,88-1,00 (m, 2H), 1,15-1,27 (m, 3H), 1,55-1,65 (m, 1H), 2,07 (s, 3H), 3,70 (s, 3H), 3,80-3,95 (m, 2H), 5,95 (s, 1H),
30 6,64 (s, 1H), 6,90-7,10 (m, 1H), 7,40-7,60 (m, 3H), 7,72 (s, 1H), 8,34 (s, 1H), 9,47 (s, 1H), 11,88 (s a, 1H). LC-MS [M+H]⁺ = 407,3.

Intermedio 122-(2-Cloro-5-isopropenil-piridin-4-ilamino)-N-metil-benzamida

En un tubo se desgasificó una solución de pinacol éster del ácido isopropenilborónico (3,31 ml, 17,6 mmol, 3 equiv.) en tolueno (200 ml) con N₂ a 50°C durante 15 min. A esto se le añadieron Pd(PPh₃)₄ (0,68 g, 0,59 mmol, 0,1 equiv.) y 2-(5-bromo-2-cloro-piridin-4-ilamino)-N-metil-benzamida (2 g, 5,87 mmol, 1 equiv.). Esta mezcla se desgasificó de nuevo con N₂ durante 30 min. A la mezcla anterior se le añadió en una porción una solución desgasificada de K₃PO₄ (4,98 g, 23,48 mmol, 4 equiv.) en H₂O (8 ml) y la mezcla resultante se calentó a 110°C durante una noche. Después de que se completara la reacción, se dejó enfriar a temperatura ambiente y el disolvente se retiró a presión reducida para producir el producto en bruto. Se purificó por cromatografía en columna sobre gel de sílice (malla 60-120) usando MeOH al 0,5%-DCM como eluyente para dar el compuesto del título en forma de un sólido de color blanquecino (0,8 g, 45%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 2,06 (s, 3H), 2,73-2,74 (d, 3H, *J* = 4,52 Hz), 5,14 (s, 1H), 5,46 (s, 1H), 7,04-7,15 (m, 2H), 7,45-7,60 (m, 2H), 7,64-7,71 (m, 1H), 7,96 (s, 1H), 8,60-8,72 (s a, 1H), 9,87 (s, 1H). LC-MS [M+H]⁺ = 302,2.

Ejemplo 57

20 2-[2-(2,5-Dimetil-2H-pirazol-3-ilamino)-5-isopropenil-piridin-4-ilamino]-N-metil-benzamida

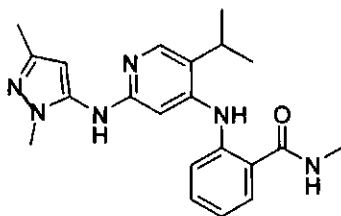


A un tubo para microondas de 10 ml se le añadieron 2-(2-cloro-5-isopropenil-piridin-4-ilamino)-N-metil-benzamida (0,075 g, 0,25 mmol, 1 equiv.), 2,5-dimetil-2H-pirazol-3-ilamina (0,055 g, 0,50 mmol, 2 equiv.), Cs₂CO₃ (0,24 g, 0,74 mmol, 3 equiv.) y 1,4-dioxano (3 ml). La mezcla resultante se desgasificó con N₂ durante 30 minutos. Después, se añadieron Pd(OAc)₂ (0,015 g, 0,07 mmol, 0,27

equiv.) y BINAP (0,046 g, 0,074 mmol, 0,3 equiv.) y la mezcla se desgasificó de nuevo con N₂ durante 10 minutos más. La mezcla de reacción resultante se irradió en un microondas CEM a 110°C y a 150 W durante 45 min. El progreso de la reacción se controló por LCMS. Después de que se completara, el Cs₂CO₃ se retiró por filtración y el filtrado se concentró a presión reducida. El producto en bruto resultante se purificó por cromatografía en columna sobre alúmina neutra usando MeOH al 0,2%-DCM como eluyente. Esto dio el compuesto del título en forma de un sólido de color blanquecino (180 mg, 48%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 2,02-2,10 (m, 6H), 2,73-2,74 (d, 3H, *J* = 4,48 Hz), 3,53 (s, 3H), 5,05 (s, 1H), 5,31 (s, 1H), 5,97 (s, 1H), 6,67 (s, 1H), 6,90-7,05 (m, 1H), 7,4-7,55 (m, 2H), 7,61-7,63 (d, 1H, *J* = 7,04 Hz), 7,76 (s, 1H), 8,48 (s, 1H), 8,54-8,67 (s a, 1H), 9,61 (s, 1H). LC-MS [M+H]⁺ = 377,4.

Ejemplo 58

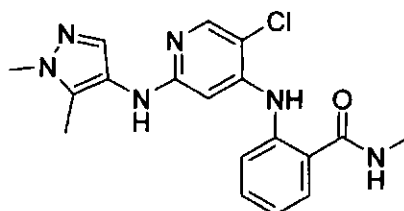
2-[2-(2,5-Dimetil-2*H*-pirazol-3-ilamino)-5-isopropil-piridin-4-ilamino]-*N*-metilbenzamida



Una solución de 2-[2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-5-isopropenil-piridin-4-ilamino]-*N*-metil-benzamida (0,13 g, 0,345 mmol, 1 equiv.) en etanol (10 ml) se desgasificó con N₂ y a esto se le añadió PtO₂ (0,012 g, 0,052 mmol, 0,15 equiv.). La mezcla resultante se agitó a temperatura ambiente en una atmósfera de H₂ con presión de globo durante 10 h. Después de que se completara la reacción, se filtró a través de un lecho de celite que después se lavó con etanol (10 ml). El filtrado se evaporó a presión reducida para dar un residuo sólido que se purificó por lavado con éter dietílico para dar el compuesto del título en forma de un sólido de color gris (80 mg, 61%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 1,24-1,26 (d, 6H, *J* = 6,76 Hz), 2,05 (s, 3H), 2,75-2,76 (d, 3H, *J* = 4,48 Hz), 2,89-3,10 (m, 1H), 3,53 (s, 3H), 5,96 (s, 1H), 6,67 (s, 1H), 6,85-7,10 (m, 1H), 7,40-7,50 (m, 2H), 7,65-7,67 (d, 1H, *J* = 7,76 Hz), 7,86 (s, 1H), 8,36 (s, 1H), 8,60-8,70 (s a, 1H), 9,89 (s, 1H). LC-MS [M+H]⁺ = 379,2.

Ejemplo 59

2-[(5-Cloro-2-[(1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil)amino]-*N*-metilbenzamida



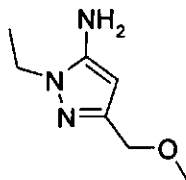
A un tubo de 10 ml que puede cerrarse herméticamente se le añadieron 2-
 [(2,5-dicloro-4-piridinil)amino]-N-metilbenzamida (95 mg, 0,321 mmol), 1,5-dimetil-
 1H-pirazol-4-amina (35,7 mg, 0,321 mmol), BINAP (20 mg, 0,032 mmol), carbonato
 5 de cesio (314 mg, 0,964 mmol) y acetato de paladio (II) (7,21 mg, 0,032 mmol) en
 1,4-dioxano (5 ml). El recipiente de reacción se cerró herméticamente y se calentó a
 150°C durante 1 h. La mezcla de reacción se purificó usando una HPLC prep (ácido
 fórmico al 0,1%, agua de 5 al 95%:acetonitrilo). Las fracciones se combinaron y se
 evaporaron. Se aisló 2-((5-cloro-2-((1,5-dimetil-1H-pirazol-4-il)amino)-4-
 10 piridinil)amino)-N-metilbenzamida (16 mg, 0,037 mmol, rendimiento de 11,38%) en
 forma de un aceite de color amarillo

LCMS (M+H)⁺ = 371,1; ¹H RMN (400 MHz, MeOD) δ ppm 2,17 (s, 3 H) 2,91 (s, 3
 H) 3,78 (s, 3 H) 6,47 (s, 1 H) 7,13 - 7,24 (m, 1 H) 7,40 (s, 1 H) 7,46 - 7,57 (m, 2 H)
 7,67 (dd, J = 7,83, 1,26 Hz, 1 H) 7,82 (s, 1 H).

15 Ejemplo 60

2-((5-Cloro-2-((1-etil-3-((metiloxi)metil)-1H-pirazol-5-il)amino)-4-piridinil)amino)-N- metilbenzamida

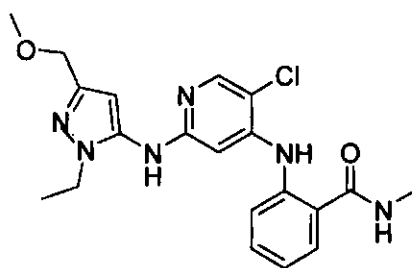
60a) 1-Etil-3-((metiloxi)metil)-1H-pirazol-5-amina



20 A un matraz de fondo redondo de 25 ml se le añadieron 4-(metiloxi)-3-
 oxobutanonitrilo (500 mg, 4,42 mmol), etil hidrazina (655 mg, 4,42 mmol) y HCl 2 M
 (2,210 ml, 4,42 mmol) en etanol (10 ml). La mezcla de reacción se agitó a
 temperatura ambiente durante una noche. Después, la mezcla de reacción se
 evaporó y se repartió entre 20 ml de acetato de etilo y 20 ml de Na₂CO₃ 1 M. La
 25 capa orgánica se lavó con salmuera, se filtró y se evaporó para obtener 1-etil-3-
 [(metiloxi)metil]-1H-pirazol-5-amina (450 mg, 2,465 mmol, rendimiento de 55,8%) en
 forma de un aceite de color amarillo. El producto se usó en la siguiente etapa sin
 purificación adicional. LCMS (M+H)⁺ = 156,1; ¹H RMN (400 MHz, DMSO-d₆) δ ppm

1,20 (t, J = 7,20 Hz, 3 H) 3,19 (s, 3 H) 3,82 (c, J = 7,33 Hz, 2 H) 4,11 (s, 2 H) 5,11 (s, 2 H) 5,22 (s, 1 H).

60b) 2-[[5-cloro-2-([1-etil-3-[(metiloxi)metil]-1H-pirazol-5-il)amino]-4-piridinil]amino]-N-metilbenzamida



5

El compuesto del título se preparó sustancialmente como se ha escrito en el Ejemplo 59 con la excepción de que se usó 1-etil-3-[(metiloxi)metil]-1H-pirazol-5-amina en lugar de 5-amino-1-metil-1H-pirazol. LCMS (M+H)⁺ = 415,1 (M+H); 1H RMN (400 MHz, DMSO-d₆) δ ppm 1,24 (t, J = 7,20 Hz, 3 H) 2,78 (d, J = 4,55 Hz, 3 H) 3,23 (s, 3 H) 3,95 (c, J = 7,07 Hz, 2 H) 4,25 (s, 2 H) 6,20 (s, 1 H) 6,77 (s, 1 H) 7,05 - 7,16 (m, 1 H) 7,44 - 7,60 (m, 2 H) 7,70 (dd, J = 7,83, 1,26 Hz, 1 H) 8,01 (s, 1 H) 8,63 (s, 1 H) 8,69 (c, J = 4,29 Hz, 1 H) 10,12 (s, 1 H).

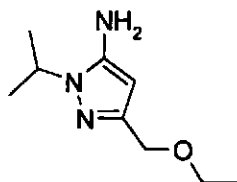
10

Ejemplo 61

2-[(5-Cloro-2-[3-[(etiloxi)metil]-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil]amino]-N-metilbenzamida

15

61a) 3-[(Etiloxi)metil]-1-(1-metiletil)-1H-pirazol-5-amina



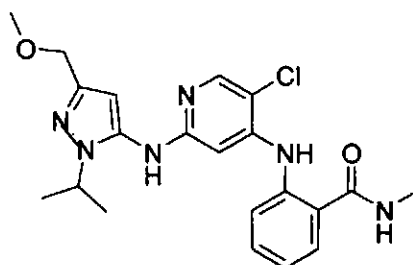
A un matraz de fondo redondo de 25 ml se le añadieron 4-(etiloxi)-3-oxobutanonitrilo (550 mg, 4,33 mmol), hidrocloreuro de isopropil hidrazina (478 mg, 4,33 mmol) y HCl (2,163 ml, 4,33 mmol) en Etanol (10 ml). La mezcla de reacción se agitó a temperatura ambiente durante una noche. Después, la mezcla de reacción se evaporó y se repartió entre 20 ml de acetato de etilo y 20 ml de Na₂CO₃ 1 M. La capa orgánica se lavó con salmuera, se filtró y se evaporó. Se aisló 3-[(etiloxi)metil]-1-(1-metiletil)-1H-pirazol-5-amina (520 mg, 2,84 mmol, rendimiento de 65,6%) en forma de un aceite de color amarillo. El producto se usó en la siguiente etapa sin purificación adicional. 1H RMN (400 MHz, DMSO-d₆) δ ppm 1,09 (t, J = 7,07 Hz, 3 H) 1,26 (d, J = 6,57 Hz, 6 H) 3,40 (c, J = 6,91 Hz, 2 H) 4,16 (s, 2 H) 4,32

20

25

(quintuplete, $J = 6,57$ Hz, 1 H) 5,06 (s, 2 H) 5,22 (s, 1 H)

61b) 2-[(5-Cloro-2-{[3-(etiloxi)metil]-1-(1-metiletil)-1H-pirazol-5-il]amino}-4-piridinil)amino]-N-metilbenzamida

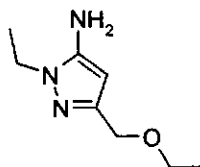


5 El compuesto del título se preparó sustancialmente como se ha escrito en el Ejemplo 59 con la excepción de que se usó 3-[(etiloxi)metil]-1-(1-metiletil)-1H-pirazol-5-amina en lugar de 5-amino-1-metil-1H-pirazol. LCMS (ES) $m/z = 443,1$ (M+H); ^1H RMN (400 MHz, MeOD) δ ppm 1,21 (t, $J = 7,07$ Hz, 3 H) 1,40 (d, $J = 6,82$ Hz, 6 H) 2,91 (s, 3 H) 3,56 (c, $J = 6,91$ Hz, 2 H) 4,45 (s, 2 H) 4,53 (quintuplete, $J =$
10 6,69 Hz, 1 H) 6,17 (s, 1 H) 6,60 (s, 1 H) 7,05 - 7,18 (m, 1 H) 7,40 - 7,56 (m, 2 H) 7,62 - 7,70 (m, 1 H) 7,92 (s, 1 H)

Ejemplo 62

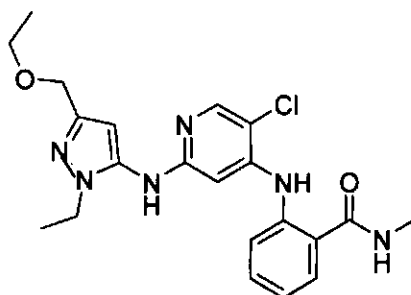
2-[(5-Cloro-2-{[1-etil-3-(etiloxi)metil]-1H-pirazol-5-il]amino}-4-piridinil)amino]-N-metilbenzamida

15 **62a) 1-Etil-3-[(etiloxi)metil]-1H-pirazol-5-amina**



A un matraz de fondo redondo de 25 ml se le añadieron 4-(etiloxi)-3-oxobutanonitrilo (550 mg, 4,33 mmol), oxalato de etil hidrazina (641 mg, 4,33 mmol) y HCl (2,163 ml, 4,33 mmol) en etanol (10 ml). La mezcla de reacción se agitó a
20 temperatura ambiente durante una noche. Después, la mezcla de reacción se evaporó y se repartió entre 20 ml de acetato de etilo y 20 ml de Na_2CO_3 1 M. La capa orgánica se lavó con salmuera, se filtró y se evaporó. Se aisló 1-etil-3-[(etiloxi)metil]-1H-pirazol-5-amina (420 mg, 2,234 mmol, rendimiento de 51,6%) en
25 forma de un aceite de color amarillo. El producto se usó en la siguiente etapa sin purificación adicional. LCMS (M+H) $^+ = 170,1$ (M+H); ^1H RMN (400 MHz, DMSO- d_6) δ ppm 1,08 (t, $J = 6,95$ Hz, 3 H) 1,19 (t, $J = 7,07$ Hz, 3 H) 3,37 - 3,43 (m, 2 H) 3,81 (c, $J = 7,24$ Hz, 2 H) 4,15 (s, 2 H) 5,09 (s, 2 H) 5,22 (s, 1 H).

62b) 2-([5-Cloro-2-((1-etil-3-[(etiloxi)metil]-1H-pirazol-5-il)amino)-4-piridinil]amino)-N-metilbenzamida

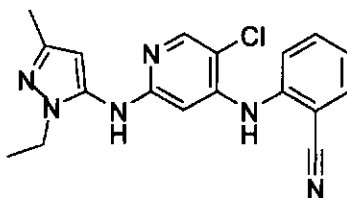


El compuesto del título se preparó sustancialmente como se ha escrito en el
Ejemplo 59 con la excepción de que se usó 1-etil-3-[(etiloxi)metil]-1H-pirazol-5-
amina en lugar de 5-amino-1-metil-1H-pirazol. LCMS (M+H)⁺ = 429,1 (M+H); 1H
RMN (400 MHz, MeOD) δ ppm 1,21 (t, J = 7,07 Hz, 3 H) 1,34 (t, J = 7,33 Hz, 3 H)
2,91 (s, 3 H) 3,55 (c, J = 6,91 Hz, 2 H) 4,04 (c, J = 7,33 Hz, 2 H) 4,43 (s, 2 H) 6,22
(s, 1 H) 6,66 (s, 1 H) 7,10 - 7,20 (m, 1 H) 7,45 - 7,53 (m, 1 H) 7,53 - 7,58 (m, 1 H)
7,66 (dd, J = 7,83, 1,52 Hz, 1 H) 7,93 (s, 1 H).

Ejemplo 63

2-([5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil]amino)-N-hidroxi-N-
metilbenzamida

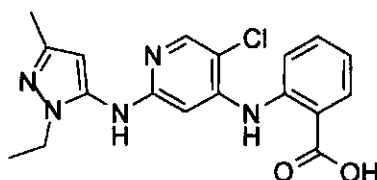
63a) 2-([5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil]amino)benzonitrilo



A un tubo de 50 ml se le añadieron 2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (738 mg, 2,80 mmol), 1-etil-3-metil-1H-pirazol-5-amina (350 mg, 2,80 mmol), BINAP (696 mg, 1,118 mmol), carbonato de cesio (2733 mg, 8,39 mmol) y acetato de paladio (II) (62,8 mg, 0,280 mmol) en 1,4-dioxano (15 ml). La mezcla de reacción se calentó a 120°C durante 18 h. El sólido se retiró por filtración y se desechó y la solución se concentró. Después, el producto se disolvió en HCl 1 M (1 ml) y se extrajo con EtOAc. La capa orgánica se desechó. la capa de agua se neutralizó con NaOH 1 M (a un valor de pH de 8) y se extrajo con EtOAc. La capa orgánica se separó, se lavó con salmuera, se secó sobre MgSO₄, se filtró y se evaporó. El sólido se disolvió en 20 ml de EtOAc y se añadieron 20 ml de agua y

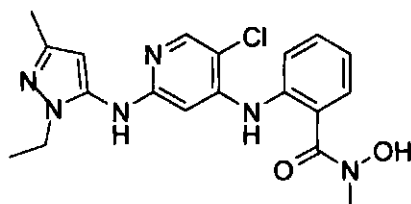
1 ml de ácido acético. La capa orgánica se separó, se lavó con salmuera, se secó sobre MgSO_4 , se filtró y se evaporó. Se aisló 2-({5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)benzonitrilo (450 mg, 1,275 mmol, rendimiento de 45,6%) en forma de una espuma de color naranja. Este producto se usó en la siguiente etapa sin purificación adicional. LCMS $(\text{M}+\text{H})^+ = 353,1$; ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ ppm 1,19 (t, $J = 7,20$ Hz, 3 H) 1,91 (s, 3 H) 3,84 (c, $J = 7,24$ Hz, 2 H) 5,92 (s, 1 H) 6,03 (s, 1 H) 7,41 (td, $J = 7,64$, 0,88 Hz, 1 H) 7,48 (d, $J = 8,08$ Hz, 1 H) 7,76 (td, $J = 7,83$, 1,52 Hz, 1 H) 7,91 (dd, $J = 7,83$, 1,52 Hz, 1 H) 7,96 (s, 1 H) 8,47 (d, $J = 7,07$ Hz, 1 H) 11,98 (s a, 1 H)

10 63b) Ácido 2-({5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)benzoico



A un matraz de fondo redondo de 50 ml se le añadieron 2-({5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)benzonitrilo (300 mg, 0,850 mmol) y una solución 1 M de NaOH (10 ml, 10,00 mmol) en 1,4-dioxano (10 ml). La mezcla se calentó a reflujo durante 18 horas. Se añadió acetato de etilo (20 ml) y las capas se separaron - todo el producto permaneció en la fase de agua. La fase de agua se neutralizó con HCl 6 N y se añadieron 40 ml de acetato de etilo. La capa orgánica se separó, se lavó con salmuera, se secó sobre MgSO_4 , se filtró y se evaporó. Se aisló ácido 2-({5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)benzoico (220 mg, 0,562 mmol, rendimiento de 66,1%) en forma de un sólido de color blanquecino y se usó en la siguiente etapa sin purificación adicional. LCMS $(\text{M}+\text{H})^+ = 372,1$; ^1H RMN (400 MHz, MeOD) δ ppm 1,33 (t, $J = 7,20$ Hz, 4 H) 2,22 (s, 3 H) 4,00 (c, $J = 7,33$ Hz, 2 H) 6,01 (s, 1 H) 6,82 (s, 1 H) 7,06 (td, $J = 7,52$, 1,14 Hz, 1 H) 7,39 - 7,49 (m, 1 H) 7,49 - 7,55 (m, 1 H) 7,87 - 7,94 (m, 1 H) 8,05 (dd, $J = 7,83$, 1,52 Hz, 1 H).

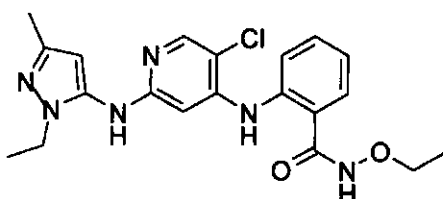
20 63c) 2-({5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-hidroxi-N-metilbenzamida



Una solución de ácido 2-((5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino)benzoico (55 mg, 0,148 mmol), HOBT (22,65 mg, 0,148 mmol) y EDC (28,4 mg, 0,148 mmol) en N,N-dimetilformamida (DMF) (5 ml) se agitó en una atmósfera de nitrógeno a temp. ambiente durante 30 minutos. A esta solución se le añadió N-metilhidroxilamina (12,35 mg, 0,148 mmol) y la solución se agitó durante 15 minutos más. La mezcla de reacción se enfrió a 5°C y se añadió gota a gota DIEA (0,052 ml, 0,296 mmol). Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante una noche. La mezcla de reacción se purificó usando HPLC preparativa (ácido fórmico al 0,1%, agua de 5 a 95%:acetonitrilo). Las fracciones se combinaron y se evaporaron. Se aisló 2-((5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino)-N-hidroxi-N-metilbenzamida (16 mg, 0,034 mmol, rendimiento de 23,05%) en forma de un sólido de color blanco. LCMS (M+H)⁺ = 401,0 (M+H); 1H RMN (400 MHz, MeOD) δ ppm 1,30 (t, J = 7,20 Hz, 3 H) 2,19 (s, 3 H) 3,37 (d, J = 1,52 Hz, 3 H) 3,96 (c, J = 7,07 Hz, 2 H) 5,95 (s, 1 H) 6,32 (s, 1 H) 7,21 - 7,33 (m, 1 H) 7,42 - 7,53 (m, 2 H) 7,56 (d, J = 7,33 Hz, 1 H) 7,86 (s, 1 H).

Ejemplo 64

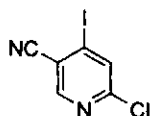
2-((5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino)-N-(etilo)benzamida



El compuesto del título se preparó sustancialmente como se ha escrito en el Ejemplo 63 con la excepción de que se usó hidrocloreto de O-etilhidroxilamina en lugar de N-metilhidroxilamina. LCMS (M+H)⁺ = 415,1 (M+H); 1H RMN (400 MHz, MeOD) δ ppm 1,23 - 1,42 (m, 6 H) 2,21 (s, 3 H) 3,87 - 4,10 (m, 4 H) 5,99 (s, 1 H) 6,59 (s, 1 H) 7,11 - 7,28 (m, 1 H) 7,46 - 7,71 (m, 3 H) 7,92 (s, 1 H).

Intermedio 13

6-Cloro-4-yodo-nicotinonitrilo

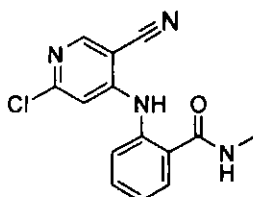


- A una mezcla de THF (100 ml) y hexano (40 ml) en atmósfera de nitrógeno se le añadió DIPA (22,21 ml, 158,78 mmol, 1,1 equiv.). La mezcla se enfrió a -80°C y a esto se le añadió gota a gota *n*-BuLi (63,57 ml, 158,78 mmol, 1,1 equiv.).
- 5 Después de que se completara la adición, la mezcla resultante se dejó calentar y se agitó a -10°C durante 15 min. La mezcla de reacción se enfrió de nuevo a -80°C y se añadió gota a gota una solución de 6-cloro-nicotinonitrilo (20 g, 144,35 mmol, 1 equiv.) en THF (100 ml). La mezcla resultante se agitó a -80°C durante 1 h. Después de 1 h, se añadió en una porción una solución de yodo (43,96 g, 173,22
- 10 mmol, 1,2 equiv.) en THF (100 ml). Después de que se completara la reacción, la reacción se interrumpió con agua (100 ml) y se extrajo con éter dietílico (6 x 100 ml). Las capas orgánicas combinadas se lavaron con una solución saturada de tiosulfato sódico (2 x 100 ml), se secaron sobre sulfato sódico, se filtraron y se concentraron al vacío para dar el producto en bruto. El compuesto en bruto se
- 15 purificó por cromatografía en columna sobre gel de sílice (malla 100-200) usando acetato de etilo al 2%-hexano como eluyente para producir el compuesto del título en forma de un sólido de color ligeramente amarillo (15 g, 39%). ^1H -RMN (400 MHz, DMSO- d_6): δ 8,38 (s, 1H), 8,79 (s, 1H). LC-MS calculado para $\text{C}_6\text{H}_2\text{ClIN}_2$ (M+H) 264,90, encontrado 264,9.

20

Intermedio 14

2-(2-Cloro-5-cianopiridin-4-ilamino)-N-metilbenzamida



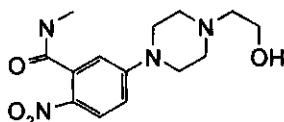
- Una mezcla de 6-cloro-4-yodo-nicotinonitrilo (14 g, 53,03 mmol, 1 equiv.), 2-amino-*N*-metoxi-benzamida (7,96 g, 53,03 mmol, 1 equiv.) y K_3PO_4 (28,14 g, 132,57
- 25 mmol, 2,5 equiv.) en 1,4-dioxano (250 ml) se desgasificó con N_2 durante 1 h. A esta mezcla se le añadieron $\text{Pd}(\text{OAc})_2$ (0,238 g, 1,06 mmol, 0,02 equiv.) y DPEPhos (2,28 g, 4,24 mmol, 0,08 equiv.). La mezcla de reacción resultante se desgasificó con N_2 durante 15 min más, después de lo cual la mezcla de reacción resultante se agitó a 110°C durante una noche. Después de que se completara la reacción, el
- 30 material sólido se recogió por filtración, se disolvió en agua (500 ml) y se extrajo

con acetato de etilo (5 x 200 ml). Las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida para dar el material en bruto. Se purificó por cromatografía en columna sobre gel de sílice (malla 60-120) usando amoníaco metanólico al 0,2% (amoníaco al 10% en MeOH) en diclorometano como eluyente para dar el compuesto del título en forma de un sólido de color amarillo pálido (9 g, 59%). ¹H-RMN (400 MHz, DMSO-*d*₆): δ 2,75 (d, 3H, *J* = 4,56 Hz), 7,09 (s, 1H), 7,25-7,35 (m, 1H), 7,53-7,60 (m, 2H), 7,72 (d, 1H, *J* = 7,48 Hz), 8,56 (s, 1H), 8,69-8,79 (s a, 1H), 10,65 (s, 1H). LC-MS calculado para C₁₄H₁₁ClN₄O (M+H) 287,06, encontrado 286,9.

10

Intermedio 15

5-[4-(2-Hidroxietil)-1-piperazinil]-N-metil-2-nitrobenzamida 3

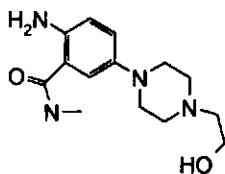


Una solución de 5-fluoro-N-metil-2-nitrobenzamida, 1-(2-hidroxietil)piperazina y base de Hunig en 20 ml de DMF se agitó a temperatura ambiente durante el fin de semana. La mezcla resultante se sometió a evaporación rotatoria a sequedad y el residuo se purificó por SF40-150 en columna ultrarrápida a MeOH al 2%-10%/CH₂Cl₂. El producto surgió en MeOH al 7%/CH₂Cl₂. MS (ES) m/e 309 [M+H].

20

Intermedio 16

2-amino-5-[4-(2-Hidroxietil)-1-piperazinil]-N-metilbenzamida 4

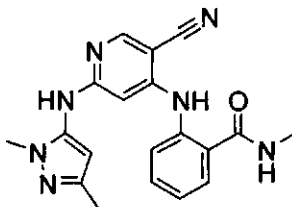


Una solución de 5-[4-(2-hidroxietil)-1-piperazinil]-N-metil-2-nitrobenzamida 3 en 250 ml de MeOH en un matraz de fondo redondo de 250 ml se agitó a temperatura ambiente en un globo de hidrógeno durante una noche. La mezcla resultante se filtró para eliminar el catalizador de Pd. El análisis por TLC en MeOH al 10%/CH₂Cl₂ no mostró más material de partida y sí un producto principal. El disolvente se sometió a evaporación rotatoria a sequedad y el residuo se usó sin purificación adicional. MS (ES) m/e 279 [M+H].

30

Ejemplo 65

2-({5-Ciano-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-

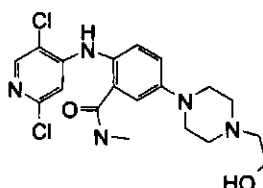
metilbenzamida

Se sintetizó 2-((5-ciano-2-((1,3-dimetil-1H-pirazol-5-yl)amino)-4-piridinil)amino)-N-metilbenzamida sustancialmente de acuerdo con el procedimiento del ejemplo 55 usando el Intermedio 15 y 5-amino-1,3-dimetilpirazol. ¹H-RMN (400 MHz, DMSO-*d*₆): δ 2,08 (d, 3H), 2,77 (d, 3H), 3,53 (s, 3H), 6,01 (s, 1H), 6,59 (s, 1H), 6,01 (s, 1H), 7,18 (t, 1H), 7,54 (t, 2H), 7,72 (d, 1H), 8,33 (s, 1H), 8,71 (d, 1H), 9,15 (s, 1H), 10,33 (s, 1H). LC-MS (M+H)⁺ = 362,0.

Ejemplo 66

10 2-[(2,5-Dicloro-4-piridinil)amino]-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida

6

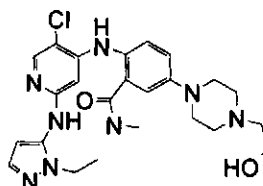


Un tubo cerrado herméticamente se cargó con 2,5-dicloro-4-yodopiridina, 2-amino-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida 4 y carbonato de cesio en 1,4-dioxano. La mezcla de reacción se desgasificó con nitrógeno durante 10 min. Al mismo tiempo, se añadieron BINAP y acetato de paladio (II) y la mezcla de reacción se calentó en 120°C en un baño de aceite durante una noche.

El análisis por TLC en EtOAc al 10%/hexano no mostró 2,5-dicloro-4-indopiridina. El análisis por TLC en MeOH al 10%/CH₂Cl₂ no mostró 2-amino-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida. El análisis por LCMS mostró que la reacción tenía un pico que podría ser el producto deseado. Mientras la temperatura de la mezcla de reacción se mantenía a aproximadamente 80°C, se filtró y el sólido se lavó con THF y CH₃CN. El sólido se filtró, se secó al vacío y se purificó con una columna ultrarrápida con MeOH al 1-8%/CH₂Cl₂, para dar el producto del título en forma de un aceite de color pardo. MS (ES) m/e 426 [M+2H].

Ejemplo 67

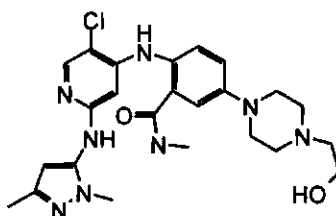
2-[(5-Cloro-2-[(1-etil-1H-pirazol-5-yl)amino]-4-piridinil)amino]-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida 9



Un tubo cerrado herméticamente se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida 6, 1-etil-1H-pirazol-5-amina y carbonato de cesio en 1,4-dioxano. La mezcla de reacción se
 5 desgasificó con nitrógeno durante 10 min. Al mismo tiempo, se añadieron BINAP y acetato de paladio (II) y la mezcla de reacción se calentó a 160°C en el microondas durante 40 minutos. El análisis por LCMS mostró un pico que se cree que era el producto deseado. El disolvente se sometió a evaporación rotatoria a sequedad y el residuo se purificó por HPLC para dar el producto del título. MS (ES) m/e 500
 10 [M+H].

Ejemplo 68

2-[(5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil)amino]-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida 10

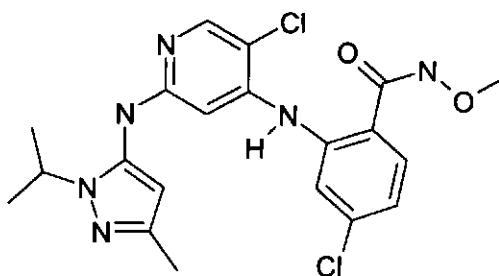


Un tubo cerrado herméticamente se cargó con 2-[(2,5-dicloro-4-piridinil)amino]-5-[4-(2-hidroxietil)-1-piperazinil]-N-metilbenzamida 6, 1-etil-1H-pirazol-5-amina y carbonato de cesio en 1,4-dioxano. La mezcla de reacción se
 15 desgasificó con nitrógeno durante 10 min. Después, se añadieron BINAP y acetato de paladio (II) y la mezcla de reacción se calentó a 160°C en el microondas durante
 20 40 minutos. El análisis por LCMS mostró el pico que se cree que corresponde al producto deseado. El disolvente se sometió a evaporación rotatoria a sequedad y el residuo se purificó por HPLC para dar el producto. MS (ES) m/e 500 [M+H].

Ejemplo 69

4-Cloro-2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-(metiloxi)benzamida

25



Etapa 1:

A una solución desgasificada de 2,5-dicloro-4-yodopiridina (4,5 g, 16,43 mmol), 2-amino-4-clorobenzonitrilo (2,507 g, 16,43 mmol) y trifosfato potásico (10,46 g, 49,3 mmol) en 1,4-dioxano (60 ml) agitada en una atmósfera de nitrógeno a temperatura ambiente se le añadieron DPEPhos (0,708 g, 1,314 mmol) y acetato de paladio (0,148 g, 0,657 mmol). La mezcla de reacción se agitó a la temperatura de reflujo durante 18 h. La mezcla de reacción se filtró. La solución se evaporó. Se añadió éter (50 ml) y el sólido formado se filtró. Se aisló 4-cloro-2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (2,8 g, 9,38 mmol, rendimiento de 57,1%) en forma de un sólido de color naranja. ^1H RMN (400 MHz, DMSO- d_6) δ ppm 6,70 (s, 1 H) 7,53 (dd, $J = 8,34, 2,02$ Hz, 1 H) 7,65 (d, $J = 2,02$ Hz, 1 H) 7,95 (d, $J = 8,34$ Hz, 1 H) 8,28 (s, 1 H) 9,12 (s a, 1 H); Tr de HPLC = 3,50 min, MS (ESI): 298,0, 300,0 $[\text{M}+\text{H}]^+$.

Etapa 2.

Se desgasificó una solución de 4-cloro-2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (2,8 g, 9,38 mmol), 3-metil-1-(1-metiletil)-1H-pirazol-5-amina (1,305 g, 9,38 mmol) y carbonato de cesio (9,17 g, 28,1 mmol) en 1,4-dioxano (40 ml). Se añadió DPEPhos (0,404 g, 0,750 mmol) seguido de acetato de paladio (0,084 g, 0,375 mmol) y la suspensión se calentó a reflujo durante una noche. El sólido se filtró, la mezcla de reacción se evaporó. El aceite de color negro se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc al 5%:DCM). Las fracciones combinadas se evaporaron. El aceite resultante se disolvió en dioxano (20 ml), se añadió hidróxido sódico (20 ml, 20,00 mmol) y la mezcla de reacción se calentó a reflujo durante una noche. Las capas se separaron y la capa orgánica se lavó con 20 ml de NaOH 1 M. Las capas acuosas se combinaron y se lavaron con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre MgSO_4 y se filtraron. La solución se evaporó, se suspendió en acetonitrilo y se filtró. Se aisló ácido 4-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzoico (260 mg, 0,619 mmol, rendimiento de 6,60%) en forma de un sólido de color amarillo. ^1H

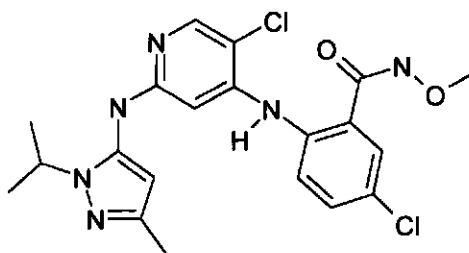
RMN (400 MHz, DMSO- d_6) δ ppm 1,28 (d, J = 6,57 Hz, 6 H) 1,91 (s, 1 H) 2,13 (s, 3 H) 4,43 (quintuplete, J = 6,57 Hz, 1 H) 5,97 (s, 1 H) 6,78 (s, 1 H) 7,05 (dd, J = 8,46, 1,89 Hz, 1 H) 7,48 (d, J = 1,77 Hz, 1 H) 7,96 (d, J = 8,34 Hz, 1 H) 8,03 (s, 1 H) 8,61 (s, 1 H); Tr de HPLC = 2,70 min, MS (ESI): 420,1, 422,0 $[M+H]^+$.

5 Etapa 3.

A la solución de ácido 4-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzoico (260 mg, 0,619 mmol) en N,N-dimetilformamida (DMF) (20 ml) se le añadieron HOBT (114 mg, 0,742 mmol) y EDC (142 mg, 0,742 mmol) y la mezcla de reacción se agitó durante 30 min. A esta
10 solución se le añadió hidrocloreuro de O-metoxilamina (62,0 mg, 0,742 mmol) y después de 30 min la reacción se enfrió a 0°C y se añadió DIEA (0,323 ml, 1,856 mmol). La mezcla de reacción se agitó a temperatura ambiente durante el fin de semana. Se añadió agua (100 ml) seguido de ácido acético (1 ml) y la mezcla de reacción se extrajo con 2 x 50 ml de acetato de etilo. La capa orgánica se lavó con
15 2 x 50 ml de $KHCO_3$ sat. y salmuera, se secó sobre $MgSO_4$ y se evaporó. El aceite de color amarillo resultante se purificó por cromatografía en columna ultrarrápida sobre gel de sílice usando DCM:EtOAc (de 10% a 100%). Se aisló 4-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida (85 mg, 0,180 mmol, rendimiento de 29,1%) en forma de una
20 espuma de color blanco. ^1H RMN (400 MHz, DMSO- d_6) δ ppm 1,27 (d, J = 6,57 Hz, 6 H) 2,12 (s, 3 H) 3,70 (s, 3 H) 4,41 (quintuplete, J = 6,57 Hz, 1 H) 5,95 (s, 1 H) 6,66 (s, 1 H) 7,01 - 7,39 (m, 1 H) 7,55 - 7,88 (m, 2 H) 8,02 (s, 1 H) 8,60 (s, 1 H) 9,76 (s a, 1 H) 12,01 (s a, 1 H); Tr de HPLC = 2,50 min, MS (ESI): 449,0, 451,1 $[M+H]^+$.

Ejemplo 70

25 4-Cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-N-(metiloxi)benzamida



Etapa 1:

A una solución desgasificada de 2,5-dicloro-4-yodopiridina (4,5 g, 16,43
30 mmol), 2-amino-5-clorobenzonitrilo (2,507 g, 16,43 mmol) y trifosfato potásico (10,46 g, 49,3 mmol) en 1,4-dioxano (60 ml) agitada en una atmósfera de nitrógeno

a temperatura ambiente se le añadieron DPEPhos (0,708 g, 1,314 mmol) y acetato de paladio (0,148 g, 0,657 mmol). La mezcla de reacción se agitó a la temperatura de reflujo durante 18 h. La mezcla de reacción se filtró. La mezcla de reacción se evaporó. Se añadió éter (50 ml) y el sólido se filtró. Se aisló 5-cloro-2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (1,8 g, 5,43 mmol, rendimiento de 33,0%) en forma de un sólido de color naranja. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 6,63 (s, 1 H) 7,52 (d, J = 8,59 Hz, 1 H) 7,81 (dd, J = 8,59, 2,53 Hz, 1 H) 8,09 (d, J = 2,53 Hz, 1 H) 8,24 (s, 1 H) 9,06 (s a, 1 H); Tr de HPLC = 3,53 min, MS (ESI): 298,0, 299,9 [M+H]⁺.

Etapas 2.

10 A una solución de 5-cloro-2-[(2,5-dicloro-4-piridinil)amino]benzonitrilo (1,8 g, 6,03 mmol) y 3-metil-1-(1-metiletil)-1H-pirazol-5-amina (0,839 g, 6,03 mmol) en 1,4-dioxano (40 ml) se le añadió carbonato de cesio (5,89 g, 18,09 mmol) y la mezcla de reacción se desgasificó. Se añadió DPEPhos (0,260 g, 0,482 mmol) seguido de acetato de paladio (0,054 g, 0,241 mmol) y la mezcla de reacción se calentó a reflujo durante una noche. Después, la suspensión se filtró. El dioxano se evaporó. El sólido se repartió entre HCl 1 M y acetato de etilo. Las capas se separaron y la capa orgánica se desechó. La capa que contenía HCl se neutralizó y se extrajo con 2 x 50 ml de acetato de etilo. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre MgSO₄, se filtraron y se evaporaron. Se aisló 5-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzonitrilo (850 mg, 2,118 mmol, rendimiento de 35,1%) en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,25 (d, J = 6,57 Hz, 6 H) 2,09 (s, 3 H) 4,35 (quintuplete, J = 6,57 Hz, 1 H) 5,89 (s, 1 H) 6,03 (s, 1 H) 7,46 (d, J = 8,84 Hz, 1 H) 7,81 (dd, J = 8,72, 2,65 Hz, 1 H) 7,96 (s, 1 H) 8,11 (d, J = 2,53 Hz, 1 H) 8,42 (s, 1 H) 8,54 (s, 1 H). Tr de HPLC = 2,60 min, MS (ESI): 400,8, 403,1 [M+H]⁺.

Etapas 3.

Una solución de 5-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzonitrilo (850 mg, 2,118 mmol) en hidróxido sódico - 1 M (20 ml, 20,00 mmol) y 1,4-dioxano (20 ml) se calentó a reflujo durante una noche. Se añadió acetato de etilo y las capas se separaron. La capa orgánica se lavó con NaOH 1 M (40 ml). Las capas acuosas combinadas se lavaron con acetato de etilo. Las capas orgánicas se combinaron, se evaporaron, se disolvieron en MeOH y se evaporaron de nuevo. Se aisló ácido 5-cloro-2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]benzoico (800 mg, 1,903 mmol, rendimiento de 90%) en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ

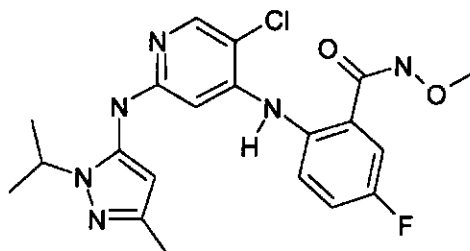
ppm 1,28 (d, J = 6,57 Hz, 6 H) 2,12 (s, 3 H) 4,40 (quintuplete, J = 6,51 Hz, 1 H) 5,97 (s, 1 H) 6,79 (s, 1 H) 7,56 - 7,62 (m, 1 H) 7,62 - 7,69 (m, 1 H) 7,94 (d, J = 2,27 Hz, 1 H) 8,04 (s, 1 H) 8,58 (s, 1 H) 9,94 (s a, 1 H) 13,97 (s a, 1 H); Tr de HPLC = 2,65 min, MS (ESI): 420,2, 421,1 [M+H]⁺.

5 Etapa 4.

A una solución de ácido 5-cloro-2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]benzoico (830 mg, 1,975 mmol) en N,N-dimetilformamida (20 ml) se le añadieron HOBT (363 mg, 2,370 mmol) y EDC (454 mg, 2,370 mmol) y la mezcla de reacción se agitó durante 30 min. A esta solución se le añadió hidrocloreuro de o-metoxilamina (198 mg, 2,370 mmol) y después de 30 min la mezcla se enfrió a 0°C. Se añadió DIEA (1,032 ml, 5,92 mmol). La mezcla de reacción se agitó a temperatura ambiente durante el fin de semana. Se añadió agua (100 ml) seguido de ácido acético (1 ml) y la solución se extrajo con 2 x 50 ml de acetato de etilo. La capa orgánica se lavó con 2 x 50 ml de KHCO₃ sat. y salmuera, se secó sobre MgSO₄ y se evaporó. El producto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice usando EtOAc:DCM (de 10% a 100%). Se aisló 5-cloro-2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-N-(metiloxi)benzamida (250 mg, 0,529 mmol, rendimiento de 26,8%) en forma de una espuma de color blanco. ¹H RMN (400 MHz, DMSO-d₆) δ ppm 1,27 (d, J = 6,57 Hz, 6 H) 2,11 (s, 3 H) 3,71 (s, 3 H) 4,20 - 4,55 (m, 1 H) 5,94 (s, 1 H) 6,63 (s, 1 H) 7,59 (s, 2 H) 7,67 (s, 1 H) 7,99 (s, 1 H) 8,50 (s, 1 H) 9,43 (s a, 1 H) 12,03 (s a, 1 H); Tr de HPLC = 2,46 min, MS (ESI): 449,1, 451,1 [M+H]⁺.

Ejemplo 71

2-[(5-Cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-5-fluoro-N-(metiloxi)benzamida



Etapa 1:

A una solución desgasificada de 2,5-dicloro-4-yodopiridina (8 g, 29,2 mmol), 2-amino-5-fluorobenzonitrilo (3,98 g, 29,2 mmol) y trifosfato potásico (18,60 g, 88 mmol) en 1,4-dioxano (100 ml) agitada en una atmósfera de nitrógeno a temperatura ambiente se le añadieron DPEPhos (1,258 g, 2,337 mmol) y acetato de

paladio (0,262 g, 1,168 mmol). La mezcla de reacción se agitó a la temperatura de reflujo durante 18 h. La mezcla de reacción se filtró. El disolvente se evaporó. Se añadió éter (50 ml) y el sólido se filtró. Se aisló 2-[(2,5-dicloro-4-piridinil)amino]-5-fluorobenzonitrilo (7,09 g, 25,1 mmol, rendimiento de 86%) en forma de un sólido de color naranja. ¹H RMN (400 MHz, METANOL-*d*₄) δ ppm 6,44 (s, 1 H) 7,46 - 7,58 (m, 2 H) 7,66 (dd, J = 8,08, 2,78 Hz, 1 H) 8,08 (s, 1 H); Tr de HPLC = 3,23 min, MS (ESI): 382,0, 384,19 [M+H]⁺.

Etapas 2.

A una solución de 2-[(2,5-dicloro-4-piridinil)amino]-5-fluorobenzonitrilo (7,09 g, 25,1 mmol) y 3-metil-1-(1-metiletil)-1H-pirazol-5-amina (3,5 g, 25,1 mmol) en 1,4-dioxano (100 ml) se le añadió carbonato de cesio (24,58 g, 75 mmol) y la mezcla de reacción se desgasificó. Se añadió DPEPhos (1,083 g, 2,012 mmol) seguido de acetato de paladio (0,226 g, 1,006 mmol) y la mezcla de reacción se calentó a reflujo durante una noche. Después, la suspensión se filtró. El dioxano se retiró por evaporación. El sólido se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (DCM al 10%:EtOAc). Las fracciones se recogieron y se evaporó. El aceite de color amarillo se disolvió en éter dietílico, se sonicó y se filtró. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-5-fluorobenzonitrilo (1,3 g, 3,21 mmol, rendimiento de 12,76%) en forma de un sólido de color blanco; ¹H RMN (400 MHz, METANOL-*d*₄) δ ppm 1,35 (d, J = 6,82 Hz, 6 H) 2,20 (s, 3 H) 4,43 (quintuplete, J = 6,69 Hz, 1 H) 5,82 (s, 1 H) 5,89 (s, 1 H) 7,47 - 7,57 (m, 2 H) 7,61 - 7,74 (m, 1 H) 7,88 (s, 1 H); Tr de HPLC = 2,40 min, MS (ESI): 385,2 [M+H]⁺.

Etapas 3.

Una solución de 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-5-fluorobenzonitrilo (1,3 g, 3,38 mmol) en hidróxido sódico - 1 M (10 ml, 10,00 mmol) y 1,4-dioxano (10 ml) se calentó a reflujo durante una noche. Se añadió acetato de etilo y las capas se separaron. La capa orgánica se lavó con NaOH 1 M (40 ml). Las capas acuosas combinadas se lavaron con acetato de etilo y se neutralizaron con ácido acético. El producto se aisló por filtración. Se aisló ácido 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-5-fluorobenzoico (1,1 g, 2,72 mmol, rendimiento de 27,2%) en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,27 (d, J = 6,57 Hz, 6 H) 2,11 (s, 3 H) 4,39 (quintuplete, J = 6,57 Hz, 1 H) 5,95 (s, 1 H) 6,70 (s, 1 H) 7,51 (td, J = 8,40, 3,16 Hz, 1 H) 7,61 (dd, J = 9,09, 4,80 Hz, 1 H) 7,72 (dd, J = 9,22, 3,16 Hz, 1

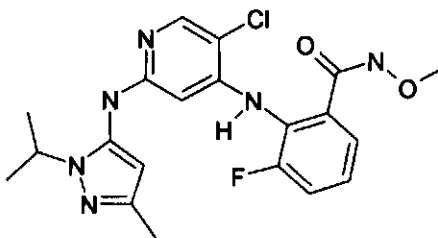
H) 8,00 (s, 1 H) 8,53 (s, 1 H) 9,66 (s a, 1 H) 13,88 (s a, 1 H); Tr de HPLC = 2,44 min, MS (ESI): 404,3 [M+H]⁺.

Etapla 4.

A la solución de ácido 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-5-fluorobenzoico (1128 mg, 2,79 mmol) en N,N-dimetilformamida (DMF) (20 ml) se le añadió HOBT (513 mg, 3,35 mmol) seguido de EDC (643 mg, 3,35 mmol) y la mezcla de reacción se agitó durante 30 min. A esta solución se le añadió hidrocloreuro de o-metoxilamina (280 mg, 3,35 mmol) y después de 30 min a 0°C se añadió DIEA (1,460 ml, 8,38 mmol). La mezcla de reacción se agitó a temperatura ambiente 24 h. Se añadió agua (100 ml) seguido de ácido acético (1 ml) y la solución se extrajo con 2 x 50 ml de acetato de etilo. La capa orgánica se separó, se lavó con 2 x 50 ml de KHCO₃ sat. y salmuera, se secó sobre MgSO₄ y se evaporó. El aceite resultante se suspendió en diclorometano y se filtró. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-5-fluoro-N-(metiloxi)benzamida (620 mg, 1,361 mmol, rendimiento de 48,7%) en forma de un sólido de color blanco. ¹H RMN (400 MHz, DMSO-d₆) δ ppm 1,26 (d, J = 6,57 Hz, 6 H) 2,10 (s, 3 H) 3,69 (s, 3 H) 4,38 (quintuplete, J = 6,57 Hz, 1 H) 5,92 (s, 1 H) 6,50 (s, 1 H) 7,41 - 7,52 (m, 2 H) 7,58 (dd, J = 8,72, 4,67 Hz, 1 H) 7,96 (s, 1 H) 8,46 (s, 1 H) 9,10 (s, 1 H) 11,95 (s, 1 H); Tr de HPLC = 2,24 min, MS (ESI): 433,4 [M+H]⁺.

Ejemplo 72

2-[(5-Cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluoro-N-(metiloxi)benzamida



25 Etapa 1:

A una solución desgasificada de 2,5-dicloro-4-yodopiridina (8 g, 29,2 mmol), 2-amino-3-fluorobenzonitrilo (3,98 g, 29,2 mmol) y trifosfato potásico (18,60 g, 88 mmol) en 1,4-dioxano (60 ml) agitada en una atmósfera de nitrógeno a temperatura ambiente se le añadieron DPEPhos (1,258 g, 2,337 mmol) y acetato de paladio (0,262 g, 1,168 mmol) La mezcla de reacción se agitó a la temperatura de reflujo durante 18 h. La mezcla de reacción se filtró. Se añadieron 3-metil-1-(1-metiletil)-

1H-pirazol-5-amina (4,07 g, 29,2 mmol) y carbonato de cesio (28,6 g, 88 mmol). La mezcla de reacción se desgasificó y se añadieron acetato de paladio (0,262 g, 1,168 mmol) y DPEPhos (1,258 g, 2,337 mmol). La mezcla de reacción se calentó a reflujo durante una noche. La mezcla de reacción se filtró y el sólido se disolvió en agua, se calentó a 50°C y se agitó durante 10 minutos y después se filtró de nuevo. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluorobenzonitrilo (6 g, 15,59 mmol, rendimiento de 53,4%) en forma de un sólido de color naranja. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,23 (d, J = 6,57 Hz, 6 H) 2,07 (s, 3 H) 4,32 (quintuplete, J = 6,57 Hz, 1 H) 5,64 (d, J = 2,02 Hz, 1 H) 5,83 (s, 1 H) 7,39 - 7,58 (m, 1 H) 7,63 - 7,82 (m, 2 H) 7,88 (s, 1 H) 8,26 (s a, 1 H) 8,41 (s a, 1 H); Tr de HPLC = 2,35 min, MS (ESI): 385,0 [M+H]⁺.

Etapas 2.

Una solución de 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluorobenzonitrilo (4,5 g, 11,69 mmol) en hidróxido sódico - 1 M (10 ml, 10,00 mmol) y 1,4-dioxano (10 ml) se calentó a reflujo durante una noche. Se añadió acetato de etilo y las capas se separaron. La capa orgánica se lavó con NaOH 1 M (40 ml). Las capas acuosas combinadas se lavaron con acetato de etilo y se neutralizaron con ácido acético. El sólido se filtró. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluorobenzoico (3,2 g, 7,53 mmol, rendimiento de 75%) se aisló en forma de un sólido de color amarillo. ¹H RMN (400 MHz, DMSO-*d*₆) δ ppm 1,24 (d, J = 6,57 Hz, 6 H) 2,09 (s, 3 H) 4,34 (quintuplete, J = 6,57 Hz, 1 H) 5,86 (s, 1 H) 5,91 (d, J = 5,81 Hz, 1 H) 7,35 (td, J = 8,02, 4,93 Hz, 1 H) 7,54 - 7,65 (m, 1 H) 7,81 (d, J = 7,58 Hz, 1 H) 7,94 (s, 1 H) 8,45 (s, 1 H) 8,88 (s a, 1 H) 13,74 (s a, 1 H); Tr de HPLC = 2,36 min, MS (ESI): 404,3 [M+H]⁺.

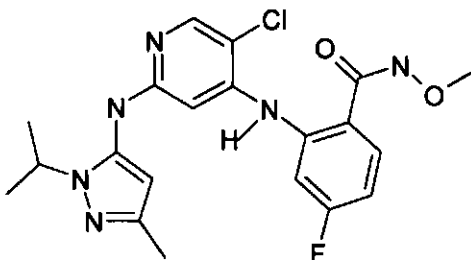
Etapas 3.

A una solución de ácido 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluorobenzoico (3,2 g, 7,92 mmol) en N,N-dimetilformamida (DMF) (50 ml) se le añadieron HOBt (1,456 g, 9,51 mmol) y EDC (1,823 g, 9,51 mmol) y la mezcla de reacción se agitó durante 30 min. A esta solución se le añadió hidrocloreto de O-metoxilamina (0,794 g, 9,51 mmol). Después de 30 min, la mezcla de reacción se enfrió a 0°C y se añadió DIEA (4,14 ml, 23,77 mmol). La mezcla de reacción se agitó a temperatura ambiente 24 h. Se añadió agua (100 ml) seguido de ácido acético (1 ml) y la solución se extrajo con 2 x 50 ml de acetato de etilo. Las capas orgánicas combinadas se lavaron con 2 x 50

ml de KHCO_3 sat. y salmuera, se secaron sobre MgSO_4 y se evaporaron. El aceite se suspendió en diclorometano y se filtró. Se aisló 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-3-fluoro-N-(metiloxi)benzamida (1,1 g, 2,414 mmol, rendimiento de 30,5%) en forma de un sólido de color blanco; ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ ppm 1,24 (d, $J = 6,57$ Hz, 6 H) 2,08 (s, 3 H) 3,68 (s, 3 H) 4,33 (quintuplete, $J = 6,57$ Hz, 1 H) 5,83 (d, $J = 5,05$ Hz, 1 H) 5,84 (s, 1 H) 7,30 - 7,49 (m, 2 H) 7,49 - 7,63 (m, 1 H) 7,92 (s, 1 H) 8,41 (d, $J = 4,29$ Hz, 2 H) 11,85 (s, 1 H); Tr de HPLC = 2,18 min, MS (ESI): 433,3 $[\text{M}+\text{H}]^+$.

Ejemplo 73

10 2-[(5-Cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-4-fluoro-N-(metiloxi)benzamida



Etapas 1:

A una solución desgasificada de 2,5-dicloro-4-yodopiridina (5 g, 18,26 mmol), 2-amino-4-fluorobenzonitrilo (2,485 g, 18,26 mmol) y trifosfato potásico (11,63 g, 54,8 mmol) en 1,4-dioxano (60 ml) agitada en una atmósfera de nitrógeno a temperatura ambiente se le añadieron DPEPhos (0,787 g, 1,460 mmol) y acetato de paladio (0,164 g, 0,730 mmol). La mezcla de reacción se agitó a la temperatura de reflujo durante 18 h. La mezcla de reacción se filtró. Se añadieron 3-metil-1-(1-metiletil)-1H-pirazol-5-amina (2,54 g, 18,26 mmol) y carbonato de cesio (17,84 g, 54,8 mmol). La mezcla de reacción se desgasificó y se añadieron acetato de paladio (0,164 g, 0,730 mmol) y DPEPhos (0,787 g, 1,460 mmol). La mezcla de reacción se calentó a reflujo durante una noche. La mezcla de reacción se filtró. Se añadió NaOH (60 ml, 60,0 mmol) y la mezcla de reacción se calentó a reflujo durante una noche. Se añadió acetato de etilo y las capas se separaron. Los extractos orgánicos combinados se lavaron con NaOH 1 M (40 ml). Las capas acuosas combinadas se lavaron con acetato de etilo y se neutralizaron con ácido acético. Se aisló ácido 2-[(5-cloro-2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-4-fluorobenzoico (2,5 g, 6,19 mmol, rendimiento de 33,9%) por filtración en forma de un sólido de color amarillo. ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ

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ppm 1,29 (d, $J = 6,57$ Hz, 6 H) 2,12 (s, 3 H) 4,43 (quintuplete, $J = 6,57$ Hz, 1 H) 5,99 (s, 1 H) 6,86 (s, 1 H) 6,87 - 6,93 (m, 1 H) 7,34 (dd, $J = 11,62, 2,53$ Hz, 1 H) 8,03 - 8,10 (m, 2 H) 8,62 (s, 1 H) 10,65 (s a, 1 H); Tr de HPLC = 2,57 min, MS (ESI): 404,2 $[M+H]^+$.

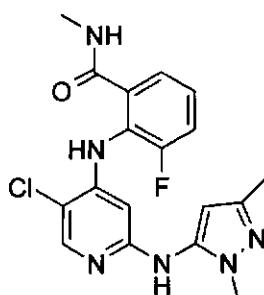
5 Etapa 2.

A una solución de ácido 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-4-fluorobenzoico (2,5 g, 6,19 mmol) en N,N-dimetilformamida (DMF) (50 ml) se le añadieron HOBT (1,138 g, 7,43 mmol) y EDC (1,424 g, 7,43 mmol) y la mezcla de reacción se agitó durante 30 min. A esta solución se le añadió hidrocloreuro de O-metoxilamina (0,620 g, 7,43 mmol) y después de 30 min la mezcla se enfrió a 0°C. Después, se añadió DIEA (3,23 ml, 18,57 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 24 h. Se añadió agua (100 ml) seguido de ácido acético (1 ml) y la solución se extrajo con 2 x 50 ml de acetato de etilo. La capa orgánica se lavó con 2 x 50 ml de $KHCO_3$ sat. y salmuera, se secó sobre $MgSO_4$ y se condensó. El aceite resultante se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (2:1 de DCM: EtOAc). Se aisló 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino)-4-piridinil]amino]-4-fluoro-N-(metiloxi)benzamida (1 g, 2,195 mmol, rendimiento de 35,5%) en forma de una espuma de color amarillo. ^1H RMN (400 MHz, $DMSO-d_6$) δ ppm 1,28 (d, $J = 6,57$ Hz, 6 H) 2,11 (s, 3 H) 3,71 (s, 3 H) 4,41 (quintuplete, $J = 6,51$ Hz, 1 H) 5,97 (s, 1 H) 6,74 (s, 1 H) 6,87 - 7,06 (m, 1 H) 7,39 (dd, $J = 11,37, 2,53$ Hz, 1 H) 7,66 (dd, $J = 8,46, 6,69$ Hz, 1 H) 8,03 (s, 1 H) 8,57 (s, 1 H) 9,96 (s a, 1 H) 11,98 (s a, 1 H); Tr de HPLC = 2,36 min, MS (ESI): 433,3 $[M+H]^+$.

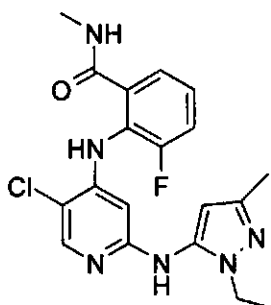
Ejemplo 74

25 Siguiendo sustancialmente el procedimiento del Ejemplo 8, los siguientes compuestos pueden prepararse partiendo con 2,5-dicloro-4-yodopiridina o 2-cloro-4-yodo-5-(trifluorometil)piridina y el 5-aminopirazol apropiadamente sustituido.

74(a). 2-[(5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il]amino)-4-piridinil]amino)-3-fluoro-N-metilbenzamida

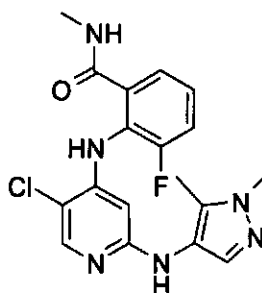


74(b). 2-({5-Cloro-2-[(1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-3-fluoro-*N*-metilbenzamida

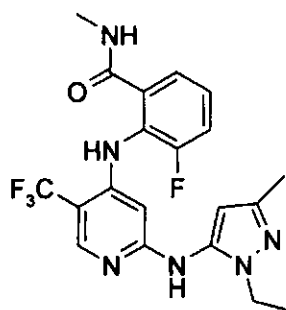


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74(c). 2-({5-Cloro-2-[(1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil}amino)-3-fluoro-*N*-metilbenzamida

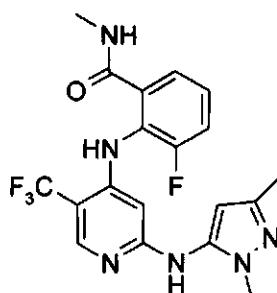


74(d). 2-([2-[(1-Etil-3-metil-1*H*-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida

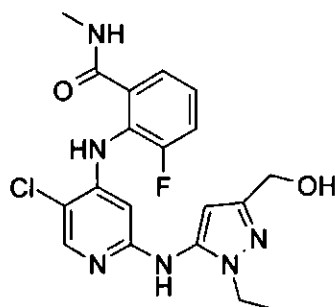


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74(e). 2-([2-[(1,3-Dimetil-1*H*-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida

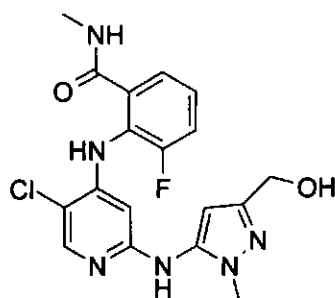


74(f). 2-[[2-[[1-Etil-3-(hidroximetil)-1H-pirazol-5-il]amino]-5-cloro-4-piridinil]amino]-3-fluoro-N-metilbenzamida

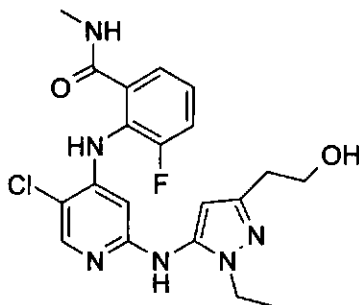


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74(g). 3-Fluoro-2-[[2-[[3-(hidroximetil)-1-metil-1H-pirazol-5-il]amino]-5-cloro-4-piridinil]amino]-N-metilbenzamida

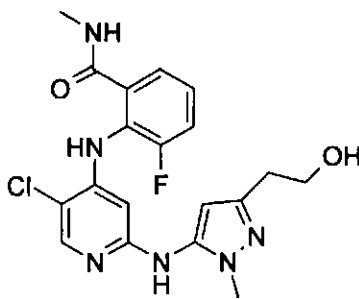


74(h). 2-[[2-[[1-Etil-3-(2-hidroxietil)-1H-pirazol-5-il]amino]-5-cloro-4-piridinil]amino]-3-fluoro-N-metilbenzamida

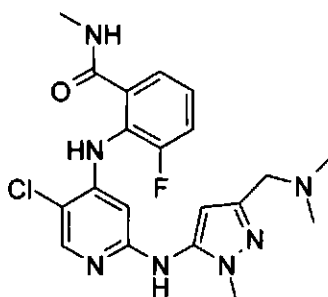


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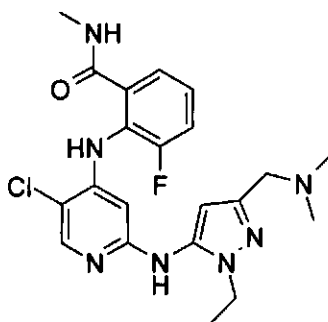
74(i). 3-Fluoro-2-[[2-[[3-(2-hidroxietil)-1-metil-1H-pirazol-5-il]amino]-5-cloro-4-piridinil]amino]-N-metilbenzamida



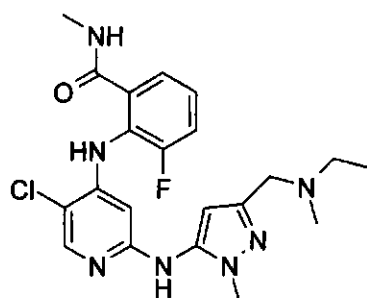
74(j). 2-([2-([3-[(Dimetilamino)metil]-1-metil-1*H*-pirazol-5-il)amino]-5-cloro-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida



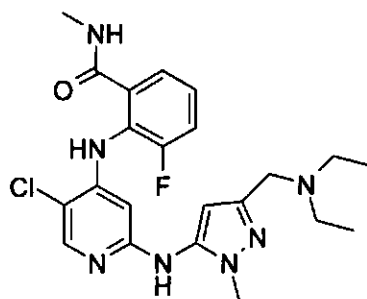
74(k). 2-([2-([3-[(Dimetilamino)metil]-1-etil-1*H*-pirazol-5-il)amino]-5-cloro-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida



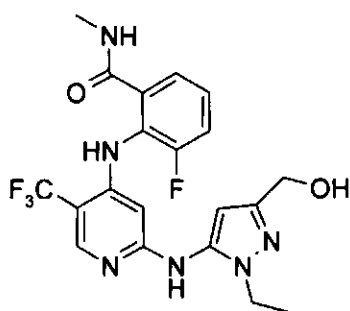
74(l). 2-([5-Cloro-2-([3-([etil(metil)amino)metil]-1-metil-1*H*-pirazol-5-il)amino]-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida



74(m). 2-([5-cloro-2-([3-[(dietilamino)metil]-1-metil-1*H*-pirazol-5-il)amino]-4-piridinil]amino)-3-fluoro-*N*-metilbenzamida

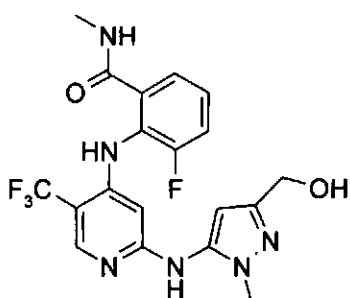


74(n). 2-([2-([1-Etil-3-(hidroximetil)-1H-pirazol-5-il]amino)-5-(trifluorometil)-4-piridinil]amino)-3-fluoro-N-metilbenzamida

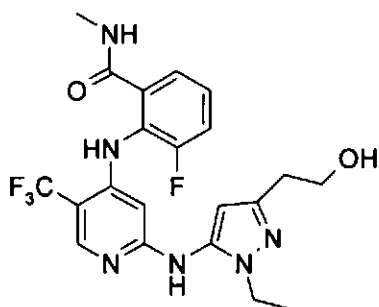


5

74(o). 3-Fluoro-2-([2-([3-(hidroximetil)-1-metil-1H-pirazol-5-il]amino)-5-(trifluorometil)-4-piridinil]amino)-N-metilbenzamida

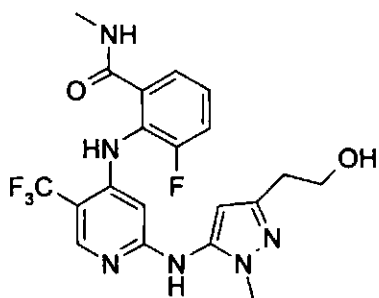


74(p). 2-([2-([1-Etil-3-(2-hidroxietil)-1H-pirazol-5-il]amino)-5-(trifluorometil)-4-piridinil]amino)-3-fluoro-N-metilbenzamida

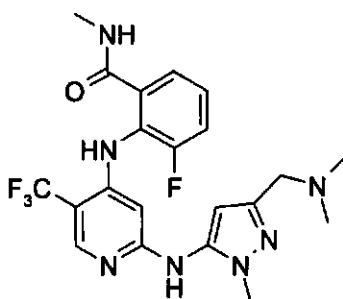


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74(q). 3-Fluoro-2-([2-([3-(2-hidroxietil)-1-metil-1H-pirazol-5-il]amino)-5-(trifluorometil)-4-piridinil]amino)-N-metilbenzamida



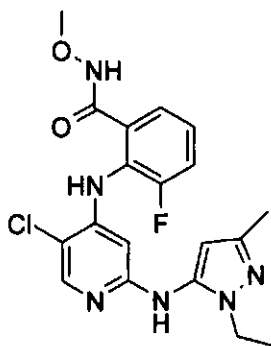
74(r). 2-([2-([3-[(Dimetilamino)metil]-1-metil-1H-pirazol-5-il]amino)-5-(trifluorometil)-4-piridinil]amino)-3-fluoro-N-metilbenzamida



Ejemplo 75

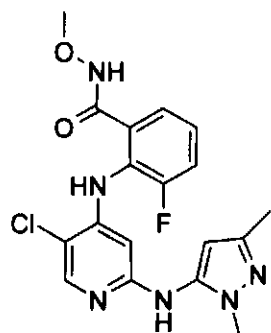
5 Siguiendo sustancialmente el procedimiento del Ejemplo 72, los siguientes compuestos pueden prepararse usando el 5-aminopirazol apropiadamente sustituido.

75(a). 2-([5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil]amino)-3-fluoro-N-(metiloxi)benzamida



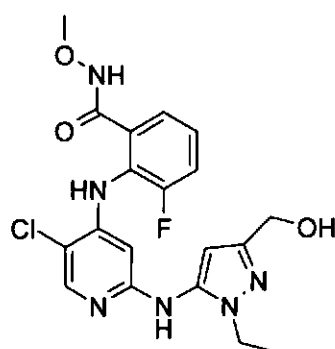
10

75(b). 2-([5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino)-3-fluoro-N-(metiloxi)benzamida

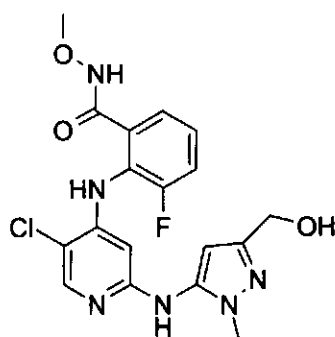


75(c). 2-([5-Cloro-2-[(1-etil-3-(hidroximetil)-1H-pirazol-5-il]amino)-4-piridinil]amino)-3-fluoro-N-(metiloxi)benzamida

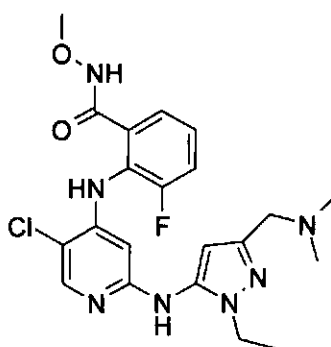
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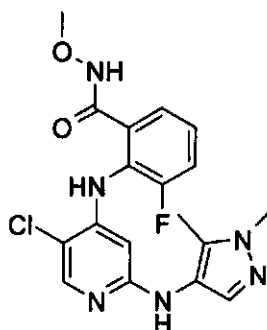
75(d). 2-[(5-Cloro-2-[(3-(hidroximetil)-1-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-3-fluoro-N-(metiloxi)benzamida



5 75(e). 2-[(5-Cloro-2-[(3-[(dimetilamino)metil]-1-etil-1H-pirazol-5-il)amino]-4-piridinil)amino]-3-fluoro-N-(metiloxi)benzamida



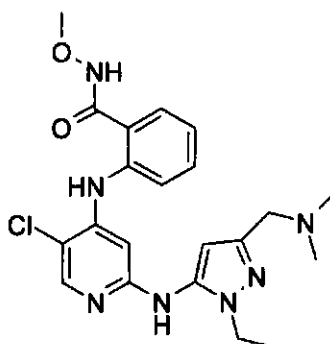
75(f). 2-[(5-Cloro-2-[(1,5-dimetil-1H-pirazol-4-il)amino]-4-piridinil)amino]-3-fluoro-N-(metiloxi)benzamida



Ejemplo 76

5 Siguiendo sustancialmente el procedimiento del Ejemplo 41a o 41b, el siguiente compuesto puede prepararse usando 3-[(dimetilamino)metil]-1-etil-1H-pirazol-5-amina.

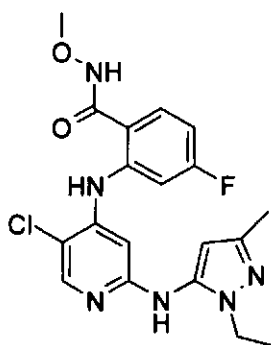
2-([5-Cloro-2-((3-[(dimetilamino)metil]-1-etil-1H-pirazol-5-il)amino)-4-piridinil]amino)-N-(metiloxi)benzamida



Ejemplo 77

10 Siguiendo sustancialmente el procedimiento del Ejemplo 73, los siguientes compuestos pueden prepararse usando el 5-aminopirazol apropiadamente sustituido.

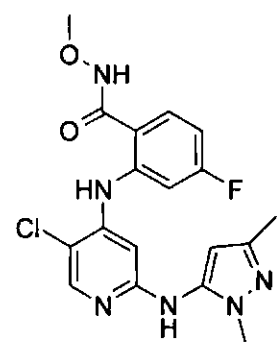
77(a). 2-([5-Cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil]amino)-4-fluoro-N-(metiloxi)benzamida



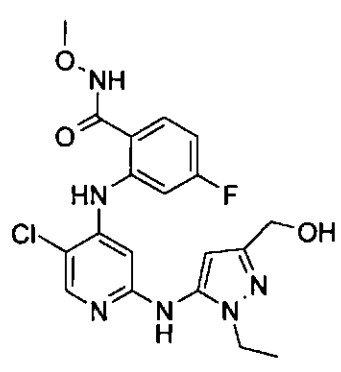
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77(b). 2-([5-Cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino)-4-fluoro-N-

(metiloxi)benzamida

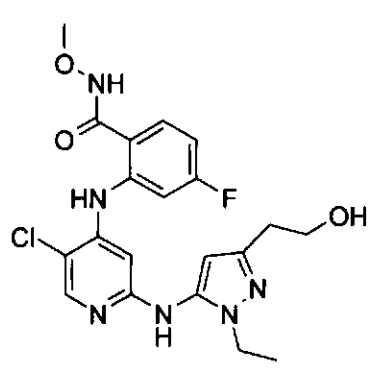


77(c). 2-[(5-Cloro-2-[[1-etil-3-(hidroximetil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-
4-fluoro-N-(metiloxi)benzamida



5

77(d). 2-[(5-Cloro-2-[[1-etil-3-(2-hidroxietil)-1H-pirazol-5-il]amino]-4-piridinil)amino]-
4-fluoro-N-(metiloxi)benzamida

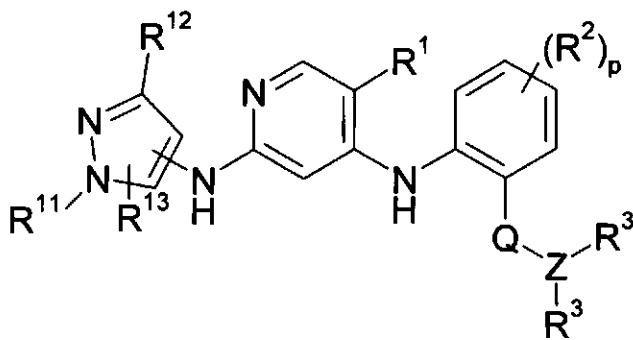


77(e). 2-[(5-Cloro-2-[[3-(hidroximetil)-1-metil-1H-pirazol-5-il]amino]-4-
piridinil)amino]-4-fluoro-N-(metiloxi)benzamida

10

REIVINDICACIONES

1. Un compuesto de fórmula (I):



5

(I)

o una sal del mismo, en el que:

R¹ es halo, CF₃, alquilo C₁-C₆, isopropenilo, (alquilenos C₂-C₆)-cicloalquilo C₃-C₆, alcoxi C₁-C₆ o ciano;

10 en R², cuando p es distinto de 0, cada R² es independientemente F, Cl, CF₃, metilo, metoxi, CH₂CF₃, -(X)_q-alquilenos C₁-C₄-R⁴, -(X-alquilenos C₁-C₄)_q-NR⁵-C(O)-R⁶, -(X-alquilenos C₁-C₄)_q-(NR⁵)_q-SO_x-R⁷, -(X-alquilenos C₁-C₄)_q-Y-N(R⁸)₂, un grupo heterocicloalquil de 5 a 6 miembros-(R⁹)_q o un grupo heteroaril de 5 a 6 miembros-(R¹⁰)_r;

15 R³ es H, cicloalquilo C₃-C₆, alquilo C₁-C₆, alcoxi C₁-C₆, alquilenos C₁-C₆-R⁴, O-alquilenos C₁-C₆-R⁴, o, los grupos R³, junto con Z, forman un anillo cíclico de 5 a 6 miembros opcionalmente sustituido con metilo, alquilenos C₁-C₄-R⁴ o cicloalquilo C₃-C₆;

R⁴ es H, -(Q)_q-N(R⁸)₂, OH, SH, alcoxi C₁-C₆, tioalquilo C₁-C₆ o un grupo heterocicloalquil de 5 a 6 miembros-(R⁹)_q;

20 R⁵ es H o alquilo C₁-C₆;

R⁶ es H, alquilo C₁-C₆, alcoxi C₁-C₆, N(R⁸)₂ o un grupo heteroaril de 5 a 6 miembros-(R¹⁰)_r;

R⁷ es alquilo C₁-C₆, fenil-(R⁹)_q o heteroaril de 5 a 6 miembros-(R¹⁰)_r;

25 R⁸ es independientemente H, alquilo C₁-C₆, -O-alquilo C₁-C₆ o, junto con el átomo de nitrógeno al que están unidos, forman un grupo heterocicloalquilo de 5 ó 6 miembros;

R⁹ es H, alquilo C₁-C₆, alcoxi C₁-C₆, -(Q)_q-N(R⁸)₂, -Q-alquilo C₁-C₆, -alquil C₁-C₆-R⁴ o heterocicloalquilo de 5 a 6 miembros;

R¹⁰ es H, alquilo C₁-C₆, alcoxi C₁-C₆ o -Q-alquilo C₂-C₆;

R^{11} es alquilo C_1-C_6 , CF_3 , $-CH_2CF_3$, $-(Q)_q$ -alquileo $C_1-C_4-R^4$, $-Q-N(R^8)_2$, fenil- $(R^5)_s$, un grupo heterocicloalquil de 5 a 6 miembros- $(R^9)_q$ o un grupo heteroaril de 5 a 6 miembros- $(R^{10})_r$;

R^{12} es H, alquilo C_1-C_6 , F, Cl, CF_3 , OH, CN, nitro, COOH, $-COO$ -alquilo C_1-C_6 , $-Y-N(R^8)_2$, cicloalquil $C_3-C_6-R^{14}$, $-(X)_q$ -alquileo $C_1-C_6-R^4$, $-(X$ -alquileo $C_1-C_6)_q$ - $NR^5-C(O)-R^6$, $-(X$ -alquileo $C_1-C_6)_q$ - $(NR^5)_q-SO_x-R^7$, $-(X$ -alquileo $C_1-C_6)_q$ - $Y-N(R^8)_2$, heterocicloalquil- $(R^9)_q$, heteroaril- $(R^{10})_r$ o fenil- $(R^{15})_s$;

R^{13} es H, F, Cl, alquilo C_1-C_6 o cicloalquilo C_3-C_6 ; o R^{12} y R^{13} , junto con los átomos de carbono a los que están unidos, forman un grupo carbocicloalquilo o heterocicloalquilo condensado de 5 ó 6 miembros;

R^{14} es independientemente H, alquilo C_1-C_6 , $-NR^5-SO_2-R^7$, $-Y-N(R^8)_2$ o $-(X)_q$ -alquileo $C_1-C_6-R^4$;

cada R^{15} es independientemente F, Cl, CF_3 , alquilo C_1-C_3 o alcoxi C_1-C_3 ;

p es 0, 1, 2 ó 3;

q es 0 ó 1;

r es 0, 1 ó 2;

s es 0, 1, 2 ó 3;

x es 1 ó 2;

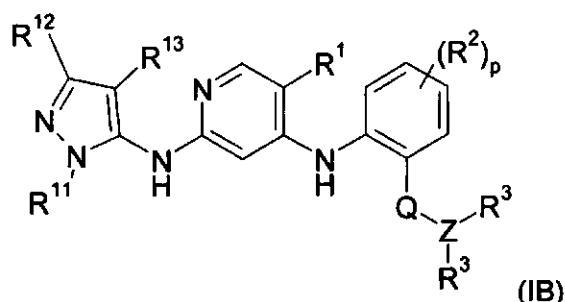
Q es $-C(O)-$, $-S(O)-$ o $-SO_2-$;

X es NR^5 , O, S, $-S(O)-$ o $-SO_2-$;

Y es un enlace, SO_2 o $C(O)$; y

Z es N o CR^5 .

2. Un compuesto de acuerdo con la reivindicación 1 que se representa por la fórmula (IB):



o una sal de mismo.

3. Un compuesto de acuerdo con la reivindicación 1 ó 2 o una sal del mismo en el que Q es $C(O)$ y Z es N.

4. El compuesto de cualquiera de las reivindicaciones 1 a 3 o una sal del mismo en el que R^3 es metoxi y el otro R^3 es H.
5. El compuesto de cualquiera de las reivindicaciones 1 a 3 o una sal del mismo en el que R^3 es metilo y el otro R^3 es H.
6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 o una sal del mismo en el que R^1 es Cl, CF_3 o CN.
7. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6 o una sal del mismo en el que p es 0 ó 1 y R^2 es F.
8. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 7 o una sal del mismo en el que R^{11} es alquilo C_1-C_3 .
9. El compuesto de cualquiera de las reivindicaciones 1 a 8 o una sal del mismo en el que R^{12} es alquilo C_1-C_4 , hidroximetilo o ciclopropilo.
10. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 9 o una sal del mismo en el que R^{13} es H.
11. Un compuesto de acuerdo con la reivindicación 1 que es:
 2-[5-cloro-2-(2-metil-5-fenil-2H-pirazol-3-ilamino)-piridin-4-ilamino]-N-metilbenzamida;
 2-({5-cloro-2-[(1-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-metilbenzamida;
 2-({5-cloro-2-[(1-etil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-metilbenzamida;
 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-N-metilbenzamida;
 2-({5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-metilbenzamida;
 2-({5-cloro-2-[(3-ciclopropil-1-metil-1H-pirazol-5-il)amino]-4-piridinil}amino)-N-metilbenzamida;

- 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-5-fluoro-*N*-metilbenzamida;
- 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-5-fluoro-*N*-metilbenzamida;
- 5 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-3-fluoro-*N*-metilbenzamida;
- 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-3-fluoro-*N*-metilbenzamida;
- 10 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-4,5-difluoro-*N*-metilbenzamida;
- 2-({5-cloro-2-[(1-etil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-4,5-difluoro-*N*-metilbenzamida;
- 5-cloro-2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 15 5-cloro-2-({5-cloro-2-[(1-etil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 2-({5-cloro-2-[(1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 2-[(5-cloro-2-[[3-(1,1-dimetiletil)-1-metil-1*H*-pirazol-5-il]amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 20 2-[(5-cloro-2-[[1-etil-3-(hidroximetil)-1*H*-pirazol-5-il]amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 2-[(5-cloro-2-[[1-(2-hidroxietil)-3-metil-1*H*-pirazol-5-il]amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 25 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-1-etil-1*H*-pirazol-3-carboxilato de etilo;
- ácido 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-1-etil-1*H*-pirazol-3-carboxílico;
- 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-1-etil-*N*-(metiloxi)-1*H*-pirazol-3-carboxamida;
- 30 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-1-etil-*N*-metil-1*H*-pirazol-3-carboxamida;
- 2-[(5-cloro-2-[[3-metil-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]amino]-4-piridinil}amino)-*N*-metilbenzamida;
- 35 2-[(5-cloro-2-[[1-(1-metil-4-piperidinil)-1*H*-pirazol-5-il]amino]-4-

- piridinil)amino]-N-metilbenzamida;
- 2-[[5-cloro-2-({1-[2-(dimetilamino)etil]-3-metil-1H-pirazol-5-il})amino]-4-piridinil]amino]-N-metilbenzamida;
- 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-N-[2-(dimetilamino)etil]-1-etil-1H-pirazol-3-carboxamida;
- 5-[[5-cloro-4-({2-[(metilamino)carbonil]fenil}amino)-2-piridinil]amino]-N-[2-(dimetilamino)etil]-1-etil-N-metil-1H-pirazol-3-carboxamida;
- 2-[[5-cloro-2-[(1,3-dimetil-1H-pirazol-4-il)amino]-4-piridinil]amino]-N-metilbenzamida;
- 10 2-[[5-cloro-2-[(1,3-dimetil-1H-pirazol-4-il)amino]-4-piridinil]amino]-N-metilbenzamida;
- 2-[[2-[(1,3-dimetil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida;
- 2-[[2-[(1-etil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida;
- 15 N-metil-2-[[2-[[3-metil-1-(1-metiletil)-1H-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]benzamida;
- 2-[[2-({1-[2-(dimetilamino)etil]-3-metil-1H-pirazol-5-il})amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida;
- 20 2-[[2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida;
- N-metil-2-[[2-[(3-metil-1-fenil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]benzamida;
- 2-[[2-[(1-(2-hidroxietil)-3-metil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil]amino]-N-metilbenzamida;
- 25 ácido 2-[[5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino]benzoico;
- 2-[[5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino]-N-(metiloxi)benzamida;
- 30 2-[[5-cloro-2-[(1, 3-dimetil-1H-pirazol-5-il) amino]-4-piridinil] amino]-N-metil-N-(metiloxi)benzamida;
- 2-[[5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil]amino]-N-[[2-(dimetilamino)etil]oxi]benzamida;
- 2-[[5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil]amino]-N-(metiloxi)benzamida;
- 35

- 2-({5-cloro-2-[(1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida;
- 2-({5-cloro-2-[(1-etil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida;
- 5 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida;
- 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida HCl;
- formiato de 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida;
- 10 2-({5-cloro-2-[(1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-etilbenzamida;
- 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-etilbenzamida;
- 15 2-({5-cloro-2-[(1-etil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-etilbenzamida;
- 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-etilbenzamida;
- 2-[(5-cloro-2-[(1-etil-3-[2-(1-pirrolidinil)etil]-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-metilbenzamida;
- 20 2-({5-cloro-2-[(1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida;
- 2-({5-cloro-2-[(1,3-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida;
- 2-[(5-cloro-2-[(4-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida;
- 25 2-({5-cloro-2-[(1-etil-4-metil-1*H*-pirazol-5-il)amino]-4-piridinil}amino)-*N*-(metiloxi)benzamida;
- 2-[(5-cloro-2-[(4-metil-1-(2-metilpropil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida;
- 30 2-[(5-cloro-2-[(3-(hidroximetil)-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino]-*N*-(metiloxi)benzamida;
- 2-[5-ciclopropil-2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-piridin-4-ilamino]-*N*-metilbenzamida;
- 2-[5-ciclopropil-2-(2-etil-5-metil-2*H*-pirazol-3-ilamino)-piridin-4-ilamino]-*N*-metilbenzamida;
- 35

- 2-[5-ciclopropil-2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-piridin-4-ilamino]-*N*-metoxi-benzamida;
- 2-[5-ciclopropil-2-(2-etil-5-metil-2*H*-pirazol-3-ilamino)-piridin-4-ilamino]-*N*-metoxi-benzamida;
- 5 2-[2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-5-isopropenil-piridin-4-ilamino]-*N*-metil-benzamida;
- 2-[2-(2,5-dimetil-2*H*-pirazol-3-ilamino)-5-isopropil-piridin-4-ilamino]-*N*-metil-benzamida;
- 10 2-([5-cloro-2-([1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 2-([5-cloro-2-([1-etil-3-((metiloxi)metil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 2-([5-cloro-2-([1-etil-3-((metiloxi)metil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 15 2-([5-cloro-2-([3-((etiloxi)metil)-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 2-([5-cloro-2-([3-((etiloxi)metil)-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 2-([5-cloro-2-([1-etil-3-((etiloxi)metil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 20 2-([5-cloro-2-([1-etil-3-((etiloxi)metil)-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 2-([5-cloro-2-([1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-hidroxi-*N*-metilbenzamida;
- 25 2-([5-cloro-2-([1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-hidroxi-*N*-metilbenzamida;
- 2-([5-cloro-2-([1-etil-3-metil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-(etiloxi)benzamida;
- 2-([5-ciano-2-([1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-*N*-metilbenzamida;
- 30 2-([5-cloro-2-([1-etil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-5-[4-(2-hidroxietil)-1-piperazinil]-*N*-metilbenzamida;
- 2-([5-cloro-2-([1,3-dimetil-1*H*-pirazol-5-il)amino]-4-piridinil)amino)-5-[4-(2-hidroxietil)-1-piperazinil]-*N*-metilbenzamida;
- 35 4-cloro-2-([5-cloro-2-([3-metil-1-(1-metiletil)-1*H*-pirazol-5-il)amino]-4-

- piridinil)amino]-N-(metiloxi)benzamida;
 4-cloro-2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-
 piridinil)amino]-N-(metiloxi)benzamida;
 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-
 5-fluoro-N-(metiloxi)benzamida;
 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-
 3-fluoro-N-(metiloxi)benzamida;
 2-[(5-cloro-2-[(3-metil-1-(1-metiletil)-1H-pirazol-5-il)amino]-4-piridinil)amino]-
 4-fluoro-N-(metiloxi)benzamida;
 2-[(5-cloro-2-[(1,3-dimetil-1H-pirazol-5-il)amino]-4-piridinil)amino]-3-fluoro-N-
 metilbenzamida;
 2-[(5-cloro-2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-4-piridinil)amino]-3-fluoro-
 N-metilbenzamida;
 2-[(5-cloro-2-[(1,5-dimetil-1H-pirazol-4-il)amino]-4-piridinil)amino]-3-fluoro-N-
 metilbenzamida;
 2-[(2-[(1-etil-3-metil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil)amino]-
 3-fluoro-N-metilbenzamida;
 2-[(2-[(1,3-dimetil-1H-pirazol-5-il)amino]-5-(trifluorometil)-4-piridinil)amino]-3-
 fluoro-N-metilbenzamida;
 2-[(2-[(1-etil-3-(hidroximetil)-1H-pirazol-5-il)amino]-5-cloro-4-piridinil)amino]-
 3-fluoro-N-metilbenzamida;
 3-fluoro-2-[(2-[(3-(hidroximetil)-1-metil-1H-pirazol-5-il)amino]-5-cloro-4-
 piridinil)amino]-N-metilbenzamida;
 2-[(2-[(1-etil-3-(2-hidroxietil)-1H-pirazol-5-il)amino]-5-cloro-4-piridinil)amino]-
 3-fluoro-N-metilbenzamida;
 3-fluoro-2-[(2-[(3-(2-hidroxietil)-1-metil-1H-pirazol-5-il)amino]-5-cloro-4-
 piridinil)amino]-N-metilbenzamida;
 2-[(2-[(3-[(dimetilamino)metil]-1-metil-1H-pirazol-5-il)amino]-5-cloro-4-
 piridinil)amino]-3-fluoro-N-metilbenzamida;
 2-[(2-[(3-[(dimetilamino)metil]-1-etil-1H-pirazol-5-il)amino]-5-cloro-4-
 piridinil)amino]-3-fluoro-N-metilbenzamida;
 2-[(5-cloro-2-[(3-[(etil(metil)amino)metil]-1-metil-1H-pirazol-5-il)amino]-4-
 piridinil)amino)-3-fluoro-N-metilbenzamida;
 2-[(5-cloro-2-[(3-[(dietilamino)metil]-1-metil-1H-pirazol-5-il)amino]-4-
 piridinil)amino)-3-fluoro-N-metilbenzamida;

- 2-[[2-[[1-etil-3-(hidroximetil)-1*H*-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]-3-fluoro-*N*-metilbenzamida;
- 3-fluoro-2-[[2-[[3-(hidroximetil)-1-metil-1*H*-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]-*N*-metilbenzamida;
- 5 2-[[2-[[1-etil-3-(2-hidroxietil)-1*H*-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]-3-fluoro-*N*-metilbenzamida;
- 3-fluoro-2-[[2-[[3-(2-hidroxietil)-1-metil-1*H*-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]-*N*-metilbenzamida;
- 10 2-[[2-[[3-[(dimetilamino)metil]-1-metil-1*H*-pirazol-5-il]amino]-5-(trifluorometil)-4-piridinil]amino]-3-fluoro-*N*-metilbenzamida;
- 2-[[5-cloro-2-[[1-etil-3-metil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[1,3-dimetil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 15 2-[[5-cloro-2-[[1-etil-3-(hidroximetil)-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[3-(hidroximetil)-1-metil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[3-[(dimetilamino)metil]-1-etil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 20 2-[[5-cloro-2-[[1,5-dimetil-1*H*-pirazol-4-il]amino]-4-piridinil]amino]-3-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[3-[(dimetilamino)metil]-1-etil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-*N*-(metiloxi)benzamida;
- 25 2-[[5-cloro-2-[[1-etil-3-metil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-4-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[1,3-dimetil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-4-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[1-etil-3-(hidroximetil)-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-4-fluoro-*N*-(metiloxi)benzamida;
- 30 2-[[5-cloro-2-[[1-etil-3-(2-hidroxietil)-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-4-fluoro-*N*-(metiloxi)benzamida;
- 2-[[5-cloro-2-[[3-(hidroximetil)-1-metil-1*H*-pirazol-5-il]amino]-4-piridinil]amino]-4-fluoro-*N*-(metiloxi)benzamida;
- 35 2-[[5-cloro-2-[[3-[(dimetilamino)metil]-1-etil-1*H*-pirazol-5-il]amino]-4-

piridinil]amino)-4-fluoro-*N*-(metiloxi)benzamida;

2-({5-cloro-2-[(1,5-dimetil-1*H*-pirazol-4-il)amino]-4-piridinil}amino)-4-fluoro-*N*-(metiloxi)benzamida; o

una sal de los mismos.

5

12. Una composición farmacéuticamente aceptable que comprende un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 11 o una sal farmacéuticamente aceptable del mismo y un excipiente farmacéuticamente aceptable.

10

13. Un método para tratar el cáncer que comprende administrar a un paciente que lo necesita una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 o una sal farmacéuticamente aceptable del mismo.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

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Applicant's or agent's file reference

P063247**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.
PCT/US 09/62163

International filing date
(day/month/year)

27 October 2009 (27.10.2009)Applicant **SMITHKLINE BEECHAM CORPORATION**

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

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 90bis.1 and 90bis.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 ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

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.
International application No. PCT/US 09/62163	International filing date (<i>day/month/year</i>) 27 October 2009 (27.10.2009)	(Earliest) Priority Date (<i>day/month/year</i>) 27 October 2008 (27.10.2008)	
Applicant SMITHKLINE BEECHAM CORPORATION			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant.
- ☐ as selected by this Authority, because the applicant failed to suggest a figure.
- ☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/62163

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10 and 12-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/82163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/535 (2010.01)

USPC - 514/236.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC - 514/236.5 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/341; 546/275.4; 546/272.1; 544/124 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: amine derivatives, treatment, cancer, angiogenesis, tyrosine kinases, VEGFR, inhibitory activity, Fak, pyridyl, pyrazolyl, carboxamide, VEGFR2, crystal structure, catalytic site, binding site, drug design, 3-dimensional models. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/007481 A2 (PATEL et al.) 22 January 2004 (22.01.2004), pg 6, ln 1 - pg 20, ln 4; pg 64, ln 20-27; pg 76, ln 24 - pg 77, ln 17; pg 85, ln 5-8.	1-3 and 11
Y	WO 00/14105 A1 (MCTIGUE et al.) 16 March 2000 (16.03.2000), pg 1, ln 5-15; pg 6, ln 25-27; pg 7, ln 28-30; pg 17, ln 10 - pg 24, ln 30; Fig 1-4; Fig 7.	1-3 and 11

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 January 2010 (15.01.2010)

Date of mailing of the international search report

13 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/62163

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/62163

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. 4-10 and 12-13

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-10 and 12-13 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-10 and 12-13 are improper multiple dependent claims because they are dependent claims which are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 4-10 and 12-13

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/62163

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3 and 11	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3 and 11	NO
Industrial applicability (IA)	Claims	1-3 and 11	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3 and 11 lack an inventive step under PCT Article 33(3) as being obvious over WO 2004/007481 A2 to Patel et al. (hereinafter Patel) in view of WO 00/14105 A1 to McTigue et al. (hereinafter McTigue).

Regarding claim 1, Patel discloses the genus of a compound of formula (I) (pg 6, ln 1 - pg 20, ln 4) where

R1 [Patel's -X-R1] (pg 6, ln 5-7), in one embodiment, may be -C(O)NH-C3-C6-cycloalkyl (pg 9, ln 13-17; pg 12, ln 6-34); when p is other than 0, each R2, in one embodiment, may be independently F, Cl, CF3, methyl or methoxy (pg 9, ln 18; pg 10, ln 5-8; pg 10, ln 27 - pg 12, ln 5);
R3 [Patel's R3], in one embodiment, may be H, C3-C6-cycloalkyl or C1-C6-alkyl (pg 10, ln 27-29; pg 17, ln 9-11);
R11, in one embodiment, may be C1-C6-alkyl, CF3 or -CH2CF3 (pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8);
R12, in one embodiment, may be H, C1-C6-alkyl, F, Cl, CF3, OH or CN (pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8);
R13, in one embodiment, may be H, F, Cl or C1-C6-alkyl (pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8);
p, in one embodiment, may be 0, 1, 2 or 3 (pg 10, ln 27-28);
Q, in one embodiment, may be -C(O)- (pg 10, ln 27-29); and
Z is N (pg 10, ln 27-29).

Such a compound possesses VEGFR inhibitory activity and is utilized in the treatment of angiogenesis related diseases, including cancer (pg 76, ln 24 - pg 77, ln 17). Patel does not expressly disclose where R1 is (C2-C6-alkylene)C3-C6-cycloalkyl. It would have been obvious to one of ordinary skill 1) to have chosen a particular species for each R1, R2, R3, R11, R12, R13, p, Q and Z based upon the resultant variation in the pyrazolylaminopyridine structure physico-chemical properties desired e.g., lipophilicity, hydrophilicity, solubility, etc. and 2) to have made such a structural variation for R1. This would have provided for pyrazolylaminopyridine structure variation in order to have optimized the resultant pharmacological activity; given such practice in the art. Further, such motivation is provided for by McTigue. McTigue discloses complete crystallization of the VEGFR-2 protein such that it may be characterized by X-ray crystallography (pg 1, ln 5-15; pg 17, ln 10 - pg 24, ln 30). The disclosed X-ray crystallographic coordinates (Fig 1-4; Fig 7) will allow generation of 3-dimensional models of the catalytic site and drug binding site of the VEGFR-2 protein (pg 7, ln 28-30), thus providing a three-dimensional description of the target for structure-based design of small molecule VEGFR-2 inhibitors as therapeutic agents (pg 6, ln 25-27). The disclosed X-ray crystallographic coordinate data of McTigue, coupled with molecular modeling software, would have enabled one of ordinary skill to have designed more selective inhibitors by varying the inhibitor's physico-chemical properties and/or molecular orientation to have provided for better inhibitor fit at the binding site; given such practice in the art.

Regarding claim 2, the combination of Patel and McTigue discloses the compound according to claim 1, as above, which is represented by the specific geometric isomer of the compound of formula (I): formula (IB) (Patel - pg 6, ln 1 - pg 8, ln 13; pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8) as shown herein where R1, R2, R3, R11, R12, R13, p, Q and Z are defined as above (Patel - pg 6, ln 1 - pg 20, ln 4; pg 84, ln 20-27; pg 85, ln 5-8; McTigue - pg 1, ln 5-15; pg 6, ln 25-27; pg 7, ln 28-30; pg 17, ln 10 - pg 24, ln 30; Fig 1-4; Fig 7).

Regarding claim 3, the combination of Patel and McTigue discloses the compound according to claim 1, as above, where Q is C(O) (Patel - pg 10, ln 27-29); and Z is N (Patel - pg 10, ln 27-29).

Regarding claim 11, the combination of Patel and McTigue discloses a compound analogous to the compound according to claim 1, as above, which is:
2-((5-chloro-2-((1-methyl-1H-pyrazol-5-yl)amino)-4-pyridinyl)amino)-N-methylbenzamide; (Patel - pg 6, ln 1 - pg 20, ln 4; pg 84, ln 20-27; pg 85, ln 5-8; McTigue - pg 1, ln 5-15; pg 6, ln 25-27; pg 7, ln 28-30; pg 17, ln 10 - pg 24, ln 30; Fig 1-4; Fig 7),

where R1 [Patel's -X-R1] (pg 6, ln 5-7) is -C(O)NH-C3-C6-cycloalkyl (Patel - pg 9, ln 13-17; pg 12, ln 6-34); R2 does not exist; p is 0 (Patel - pg 10, ln 27-28); R3 [Patel's R3] is H or -CH3 [C1-alkyl] (Patel - pg 10, ln 27-29; pg 17, ln 9-11); R11 is -CH3 [C1-alkyl] (Patel - pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8); R12 and R13 are each H (Patel - pg 16, ln 7-9; pg 17, ln 9-11; pg 84, ln 20-27; pg 85, ln 5-8); Q is -C(O)- (Patel - pg 10, ln 27-29); and Z is N (Patel - pg 10, ln 27-29).

The combination of Patel and McTigue does not expressly disclose the compound according to claim 1, as above, which is:

2-((5-chloro-2-((1-methyl-1H-pyrazol-5-yl)amino)-4-pyridinyl)amino)-N-methylbenzamide; where R1 is -Cl.

- see supplemental box -

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/62163

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-- Box No. V(2) -- Citations and explanations:

It would have been encompassed within the knowledge level of one of ordinary skill to have made such a structural variation in order to have optimized the resultant pharmacological activity; given such practice in the art. The disclosed X-ray crystallographic coordinate data of McTigue (pg 1, in 5-15; pg 6, in 25-27; pg 7, in 28-30; pg 17, in 10 - pg 24, in 30; Fig 1-4; Fig 7), coupled with molecular modeling software, would have enabled one of ordinary skill to have designed more selective inhibitors by varying the inhibitor's physico-chemical properties and/or molecular orientation to have provided for better inhibitor fit at the binding site; given such practice in the art.

Claims 1-3 and 11 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

125

PATENT COOPERATION TREATY

PCT/US2009/062163

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

KANAGY, James, M..
GLAXOSMITHKLINE
Corporate Intellectual Property, UW2220
709 Swedeland Road,
P.O. Box 1539
King Of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 13 January 2010 (13.01.2010)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU63247	
International application No. PCT/US2009/062163	International filing date (day/month/year) 27 October 2009 (27.10.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address SMITHKLINE BEECHAM CORPORATION One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101 United States of America	State of Nationality US	State of Residence US
	Telephone No. 610-270-5014	
	Facsimile No. 610-270-5090	
	E-mail address US_CIPKOP@GSK.COM	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address GLAXOSMITHKLINE LLC One Franklin Plaza 200 North 16th Street Philadelphia, PA 19102 United States of America	State of Nationality US	State of Residence US
	Telephone No. 610-270-5014	
	Facsimile No. 610-270-5090	
	E-mail address US_CIPKOP@GSK.COM ☒ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☒ the International Searching Authority	☐ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Suarez Javier e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
---	---

Facsimile No. +41 22 338 71 30

PATENT COOPERATION TREATY

PCT/US2009/062163

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:
KANAGY, James, M..
Glaxosmithkline
Corporate Intellectual Property, UW2220
709 Swedeland Road,
P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 24 June 2010 (24.06.2010)	
Applicant's or agent's file reference PU63247	IMPORTANT NOTIFICATION
International application No. PCT/US2009/062163	International filing date (day/month/year) 27 October 2009 (27.10.2009)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address XIE, Ren 250 South Collegeville Road Collegeville, PA 19426 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gallay Laurence e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
---	---

Facsimile No. +41 22 338 71 30

PATENT COOPERATION TREATY

PCT/US2009/062163

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

KANAGY, James, M..
Glaxosmithkline
Corporate Intellectual Property, UW2220
709 Swedeland Road,
P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 24 June 2010 (24.06.2010)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU63247	
International application No. PCT/US2009/062163	International filing date (day/month/year) 27 October 2009 (27.10.2009)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address PENG, Xin 250 South Collegeville Road Collegeville, PA 19426 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gallay Laurence e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
---	---

Facsimile No. +41 22 338 71 30

PATENT COOPERATION TREATY

PCT/US2009/062163

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

KANAGY, James, M..
Glaxosmithkline
Corporate Intellectual Property, UW2220
709 Swedeland Road,
P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 24 June 2010 (24.06.2010)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU63247	
International application No. PCT/US2009/062163	International filing date (day/month/year) 27 October 2009 (27.10.2009)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address MELLINGER, Mark 250 South Collegeville Road Collegeville, PA 19426 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gallay Laurence e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
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Facsimile No. +41 22 338 71 30

PATENT COOPERATION TREATY

PCT/US2009/062163

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

KANAGY, James, M..
GLAXOSMITHKLINE
Corporate Intellectual Property, UW2220
709 Swedeland Road,
P.O. Box 1539
King Of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
24 June 2010 (24.06.2010)

Applicant's or agent's file reference
PU63247

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/062163

International filing date (day/month/year)
27 October 2009 (27.10.2009)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address KASPAREC, Jiri 250 South Collegeville Road Collegeville, PA 19426 United States of America	State of Nationality CZ	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gallay Laurence e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
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Facsimile No. +41 22 338 71 30

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.	
International application No. PCT/US 09/62163	International filing date (day/month/year) 27 October 2009 (27.10.2009)	(Earliest) Priority Date (day/month/year) 27 October 2008 (27.10.2008)
Applicant SMITHKLINE BEECHAM CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/62163

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-10 and 12-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/62163

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/535 (2010.01)

USPC - 514/236.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/236.5 (see search terms below)Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/341; 546/275.4; 546/272.1; 544/124 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: amine derivatives, treatment, cancer, angiogenesis, tyrosine kinases, VEGFR, inhibitory activity, Fak, pyridyl, pyrazolyl, carboxamide, VEGFR2, crystal structure, catalytic site, binding site, drug design, 3-dimensional models. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/007481 A2 (PATEL et al.) 22 January 2004 (22.01.2004), pg 6, ln 1 - pg 20, ln 4; pg 84, ln 20-27; pg 76, ln 24 - pg 77, ln 17; pg 85, ln 5-8.	1-3 and 11
Y	WO 00/14105 A1 (MCTIGUE et al.) 16 March 2000 (16.03.2000), pg 1, ln 5-15; pg 6, ln 25-27; pg 7, ln 28-30; pg 17, ln 10 - pg 24, ln 30; Fig 1-4; Fig 7.	1-3 and 11

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 January 2010 (15.01.2010)

Date of mailing of the international search report

13 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

No. 11-058067-00000-0000

Fecha: 2011-05-11 17:17:02 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 131

PATENTE DE INVENCION ☐

MODELO DE

- ☐ Indicación que se solicita una patente.
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Descripción de la invención
 - ☐ Dibujos de ser estos pertinentes
 - ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
- Completa ☐ Incompleta ☐

PATENTE DE INVENCION PCT ☒

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

- ☒ Indicación que se solicita una PCT
 - ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
 - ☐ Dibujos de ser estos pertinentes
 - ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
- Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
 - ☐ Comprobante de pago de las tasas establecidas
- Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Representación gráfica de un esquema de trazado
 - ☐ Comprobante de pago de las tasas establecidas
- Completa ☐ Incompleta ☐



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXOSMITHKLINE LLC

REFERENCIA	Radicación No.	11 058067
	Solicitud internacional	PCT/US2009/62163
	Fecha inicio fase nacional	27/05/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

009747

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez 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 título primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

17 JUN. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha _____.
adpa11