SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-028419- -00000-0000
Fecha: 2011-03-08 16:24:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 264

PCT

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NUEVA

11-28419

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE PICOLINAMIDA COMO INHIBIDORES DE QUINAS

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 2 de marzo de 2011

P2011/000048

02-04-2011

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000048**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
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 D.C.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

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

INVENTOR (ES) (72)

Nombre: **1.** MATTHEW T. BURGER, **2.** WOOSEOK HAN, **3.** JIONG LAN, **4.** GISELE NISHGUCHI
Dirección: Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 E.U.A.
Nacionalidad o Domicilio: 1 y 4. Estadounidense 2. Koreana, 3. China

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2009/061205 Fecha Agosto 13, 2009

Publicación Internacional No. WO 2010/026124 Fecha Marzo 11, 2010

(6) **Título (54)** **DERIVADOS DE PICOLINAMIDA COMO INHIBIDORES DE QUINASA**

Clasificación Internacional (51) C07D 401/12, C07D 401/14, A61K 31/444, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 2, 2008	61/093,666
US	Julio 15, 2009	61/225,660

(9) **Comprobante de pago No.** 11- **Fecha** Marzo de 2011

(10) **ANEXOS**

[x]	Comprobante de pago de la tasa de presentación de la solicitud.
[x]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[x]	Poderes, si fuere el caso. Adjunto copia simple. Ver Exp. Nº 08-124.716
[ ]	Documento de cesión del inventor al solicitante o a su causante.
[ ]	Declaraciones.
[x]	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
[x]	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
[ ]	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
[ ]	Traducción del examen preliminar internacional efectuado por la IPEA.
[ ]	De ser el caso, copia del contrato de acceso.
[ ]	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
[ ]	De ser el caso, certificado de depósito del material biológico.
[ ]	Arte final 12 x 12.
[ ]	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
[ ]	De ser el caso, modificaciones efectuadas a la solicitud internacional.
[x]	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0021617

Bogotá D.C., Marzo 08 de 2011 - 16:06:20

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	418328035	08/03/2011	1.142.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	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. 11-028419- -00000-0000
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TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

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

5

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

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

6

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

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E-mail: treseser1@yahoo.com. No. 8346

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahín
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

NOVARTIS AG

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, 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 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975/2006

9

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by ..... M. Stachelin
3. in his/her function as ..... Kpl.
4. and certified by the seal of the ..... Gemeinden
   .....

Certified 28. Aug. 2006

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 2'049/13'384
9. Seal/stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from BURGER, Matthew T. to NOVARTIS AG, dated 24 August 2009 (24.08.2009)
VIII-2-1(iv)		an assignment from HAN, Wooseok to NOVARTIS AG, dated 20 July 2009 (20.07.2009)
VIII-2-1(iv)		an assignment from LAN, Jiong to NOVARTIS AG, dated 24 August 2009 (24.08.2009)
VIII-2-1(iv)		an assignment from NISHIGUCHI, Gisele to NOVARTIS AG, dated 24 August 2009 (24.08.2009)

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

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International Bureau

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C07D 401/12 (2006.01) *A61K 31/444* (2006.01)
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61/093,666 2 September 2008 (02.09.2008) US
61/225,660 15 July 2009 (15.07.2009) US

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BURGER, Matthew, T.** [US/US]; Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 (US). **HAN, Wooseok** [KR/US]; Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 (US). **LAN, Jiong** [CN/US]; Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 (US). **NISHIGUCHI, Gisele** [US/US]; Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 (US).

(74) Agent: **VOEGELI-LANGE, Regina**; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

(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))*

Published:

— *with international search report (Art. 21(3))*

WO 2010/026124 A1

(54) **Title**: PICOLINAMIDE DERIVATIVES AS KINASE INHIBITORS

(57) **Abstract**: New picolinamide compounds, compositions and methods of inhibition of Provirus Integration of Maloney Kinase (PIM kinase) activity associated with tumorigenesis in a human or animal subject are provided. In certain embodiments, the compounds and compositions are effective to inhibit the activity of at least one PIM kinase. The new compounds and compositions may be used either alone or in combination with at least one additional agent for the treatment of a serine/threonine kinase- or receptor tyrosine kinase- mediated disorder, such as cancer.

PICOLINAMIDE DERIVATIVES AS KINASE INHIBITORS

Cross-Reference to Related Applications

This application claims the benefit under 35 U.S.C. §119(e) to U.S. provisional application serial No. 61/093,666, filed on September 02, 2008, and to U.S. provisional application serial No. 61/225,660, filed July 15, 2009, which are incorporated herein in their entirety by reference.

FIELD OF THE INVENTION

[0001] The present invention relates to new compounds and their tautomers and stereoisomers, and pharmaceutically acceptable salts, esters, metabolites or prodrugs thereof, compositions of the new compounds together with pharmaceutically acceptable carriers, and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer.

BACKGROUND

[0002] Infection with the Maloney retrovirus and genome integration in the host cell genome results in development of lymphomas in mice. Provirus Integration of Maloney Kinase (PIM-Kinase) was identified as one of the frequent proto-oncogenes capable of being transcriptionally activated by this retrovirus integration event (Cuypers HT et al., "Murine leukemia virus-induced T-cell lymphomagenesis: integration of proviruses in a distinct chromosomal region," *Cell* **37(1):**141-50 (1984); Selten G, et al., "Proviral activation of the putative oncogene Pim-1 in MuLV induced T-cell lymphomas" *EMBO J* **4(7):**1793-8 (1985)), thus establishing a correlation between over-expression of this kinase and its oncogenic potential. Sequence homology analysis demonstrated that there are 3 highly homologous Pim-Kinases (Pim1, 2 & 3), Pim1 being the proto-oncogene originally identified by retrovirus integration. Furthermore, transgenic mice over-expressing Pim1 or Pim2 show increased incidence of T-cell lymphomas (Breuer M et al., "Very high frequency of lymphoma induction by a chemical carcinogen in pim-1 transgenic mice" *Nature* **340(6228):**61-3 (1989)), while over-expression in conjunction with c-myc is associated with incidence of B-cell lymphomas (Verbeek S et al., "Mice bearing the E mu-myc and E mu-pim-1 transgenes develop pre-B-cell leukemia

prenatally" *Mol Cell Biol* **11(2):**1176-9 (1991)). Thus, these animal models establish a strong correlation between Pim over-expression and oncogenesis in hematopoietic malignancies. In addition to these animal models, Pim over-expression has been reported in many other human malignancies. Pim1, 2 & 3 over-expression is frequently observed in many hematopoietic malignancies (Amson R et al., "The human protooncogene product p33pim is expressed during fetal hematopoiesis and in diverse leukemias," *PNAS USA* 86(22):8857-61 (1989); Cohen AM et al., "Increased expression of the hPim-2 gene in human chronic lymphocytic leukemia and non-Hodgkin lymphoma," *Leuk Lymph* 45(5):951-5 (2004), Huttmann A et al., "Gene expression signatures separate B-cell chronic lymphocytic leukaemia prognostic subgroups defined by ZAP-70 and CD38 expression status," *Leukemia* **20:**1774–1782 (2006)) and in prostate cancer (Dhanasekaran SM, et al., "Delineation of prognostic biomarkers in prostate cancer," *Nature* 412(6849):822-6 (2001); Cibull TL, et al., "Overexpression of Pim-1 during progression of prostatic adenocarcinoma," *J Clin Pathol* 59(3):285-8 (2006)), while over-expression of Pim3 is frequently observed in hepatocellular carcinoma (Fujii C, et al., "Aberrant expression of serine/threonine kinase Pim-3 in hepatocellular carcinoma development and its role in the proliferation of human hepatoma cell lines," *Int J Cancer* **114:**209–218 (2005)) and pancreatic cancer (Li YY et al., "Pim-3, a proto-oncogene with serine/threonine kinase activity, is aberrantly expressed in human pancreatic cancer and phosphorylates bad to block bad-mediated apoptosis in human pancreatic cancer cell lines," *Cancer Res* **66(13):**6741-7 (2006)).

[0003] Pim1, 2 & 3 are Serine/Threonine kinases that normally function in survival and proliferation of hematopoietic cells in response to growth factors and cytokines. Cytokines signaling through the Jak/Stat pathway leads to activation of transcription of the Pim genes and synthesis of the proteins. No further post-translational modifications are required for the Kinase Pim activity. Thus, signaling down stream is primarily controlled at the transcriptional/translational and protein turnover level. Substrates for Pim kinases include regulators of apoptosis such as the Bcl-2 family member BAD (Aho T et al., "Pim-1 kinase promotes inactivation of the pro-apoptotic Bad protein by phosphorylating it on the Ser112 gatekeeper site,: *FEBS Letters* **571**: 43–49 (2004)), cell cycle regulators such as $p21^{WFA1/CIP1}$ (Wang Z, et al., "Phosphorylation of the cell cycle inhibitor p21Cip1/WAF1 by Pim-1 kinase," *Biochem Biophys Acta* 1593:45–55 (2002)), CDC25A (1999), C-TAK (Bachmann M et al., "The Oncogenic

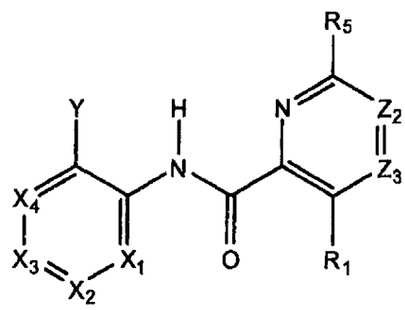
Serine/Threonine Kinase Pim-1 Phosphorylates and Inhibits the Activity of Cdc25C-associated Kinase 1 (C-TAK1). A novel role for Pim-1 at the G2/M cell cycle checkpoint," *J Biol Chem* **179**:48319-48328 (2004)) and NuMA (Bhattacharya N, et al., "Pim-1 associates with protein complexes necessary for mitosis," *Chromosoma* **111(2):**80-95 (2002)) and the protein synthesis regulator 4EBP1 (Hammerman PS et al., "Pim and Akt oncogenes are independent regulators of hematopoietic cell growth and survival," *Blood* **105(11):**4477-83 (2005)). The effects of Pim(s) in these regulators are consistent with a role in protection from apoptosis and promotion of cell proliferation and growth. Thus, over-expression of Pim(s) in cancer is thought to play a role in promoting survival and proliferation of cancer cells and, therefore, their inhibitions should be an effective way of treating cancers on which they are over-expressed. In fact several reports indicate that knocking down expression of Pim(s) with siRNA results in inhibition of proliferation and cell death (Dai JM, et al., "Antisense oligodeoxynucleotides targeting the serine/threonine kinase Pim-2 inhibited proliferation of DU-145 cells," *Acta Pharmacol Sin* **26(3):**364-8 (2005); Fujii et al. 2005; Li et al. 2006). Furthermore, mutational activation of several well know oncogenes in hematopoietic malignancies are thought exert its effects at least in part through Pim(s). For example, targeted down regulation of pim expression impairs survival of hematopoietic cells transformed by Flt3 and BCR/ABL (Adam et al. 2006). Thus, inhibitors to Pim1, 2 &3 would be useful in the treatment of these malignancies. In addition to a potential role in cancer treatment and myeloproliferative diseases, such inhibitor could be useful to control expansion of immune cells in other pathologic condition such as autoimmune diseases, allergic reactions and in organ transplantation rejection syndromes. This notion is supported by the findings that differentiation of Th1 Helper T-cells by IL-12 and IFN-α results in induction of expression of both Pim1&2 (Aho T et al., "Expression of human Pim family genes is selectively up-regulated by cytokines promoting T helper type 1, but not T helper type 2, cell differentiation," *Immunology* **116:** 82-88 (2005)). Moreover, Pim(s) expression is inhibited in both cell types by the immunosuppressive TGF-β (Aho et al. 2005). These results suggest that Pim kinases are involved in the early differentiation process of Helper T-cells, which coordinate the immunological responses in autoimmune diseases, allergic reaction and tissue transplant rejection.

[0004] A continuing need exists for compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, treat cancer, modulate cell cycle arrest, and/or

inhibit molecules such as Pim1, Pim2 and Pim3, and pharmaceutical formulations and medicaments that contain such compounds. A need also exists for methods of administering such compounds, pharmaceutical formulations, and medicaments to patients or subjects in need thereof.

SUMMARY OF INVENTION

[0005] New compounds, and their stereoisomers, tautomers and pharmaceutically acceptable salts, are provided of the Formula I



I

wherein,

X_1, X_2, X_3 and X_4 are independently selected from CR_2 and N; provided that at least one but not more than two of X_1, X_2, X_3 and X_4 are N;

Y is selected from a group consisting of cycloalkyl, partially unsaturated cycloalkyl, and heterocycloalkyl, wherein each member of said group may be substituted with up to four substituents;

Z_2 and Z_3 are independently selected from CR_{12} and N; provided that not more than one of Z_2 and Z_3 can be N;

R_1 is selected from the group consisting of hydrogen, $-NHR_3$, halo, hydroxyl, alkyl, cyano, and nitro;

R_2 and R_{12} independently at each occurrence are selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, SO_3H and substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, hetero cycloalkyl, and partially saturated cycloalkyl;

R_3 is selected from the group consisting of hydrogen, $-CO-R_4$ and substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_4 is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, and alkylamino; and

R_5 represents a group selected from substituted or unsubstituted aryl, C_3-C_7 cycloalkyl, heteroaryl, partially unsaturated cycloalkyl and alkyl, wherein each said substituted R_5 group may be substituted with up to four substituents selected from halo, cyano, amino, C_{1-4} alkyl, C_{3-6} cycloalkyl, alkoxy, nitro, carboxy, carbonyl, carboalkoxy, aminocarboxy, substituted aminocarbonyl, aminosulfonyl, substituted aminosulfonyl and alkoxyalkyl.

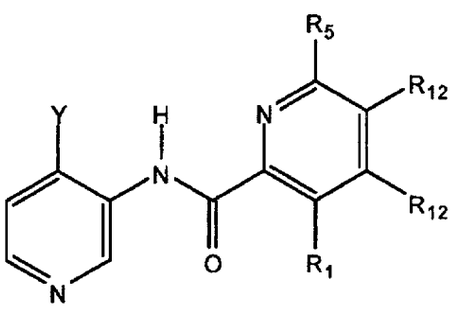
[0006] In some embodiments, new compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein X_2 is N and X_1, X_3 and X_4 are CR_2.

[0007] In some embodiments, new compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_2 is selected from hydrogen, methyl, ethyl, halo, cyano.

[0008] In some embodiments, compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Z_2 and Z_3 are CR_{12}.

[0009] In some embodiments, compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_{12} is selected from hydrogen, halo, methyl, ethyl and cyano.

[0010] In other embodiments, new compounds, and their stereoisomers, tautomers and pharmaceutically acceptable salts, are provided of the Formula II



II

wherein,

Y is selected from a group consisting of cyclohexyl, partially unsaturated cyclohexyl, and heterocyclo-C_5-alkyl, wherein each member of said group may be substituted with up to four substituents;

R_1 is selected from the group consisting of hydrogen, -NHR_3, halo, hydroxyl, alkyl, C_{3-4} cycloalkyl, cyano, and nitro;

R_{12} independently at each occurrence is selected from the group consisting of hydrogen, halo, hydroxyl, amino, nitro, cyano, SO_3H and substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, hetero cycloalkyl, and partially saturated cycloalkyl;

R_3 is selected from the group consisting of hydrogen, -CO-R_4 and substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_4 is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, and alkylamino; and

R_5 represents a group selected from hydrogen and substituted or unsubstituted alkyl, C_6-cycloalkyl, aryl and heteroaryl, wherein each said substituted R_5 group may be substituted with up to four substituents selected from halo, cyano, amino, C_{1-4} alkyl, C_{3-6} cycloalkyl, alkoxy, nitro, carboxy, carbonyl, carboalkoxy, aminocarboxy, substituted aminocarbonyl, aminosulfonyl, substituted aminosulfonyl and alkoxyalkyl.

[0011] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is selected from a group consisting of substituted or unsubstituted cycloalkyl, cycloalkenyl, piperidinyl and piperazinyl, wherein each member of said group is substituted with up to four substituents. In some embodiments, Y is substituted with up to four substituents selected from, cyano, nitro, halo, hydroxyl, amino, alkoxy, substituted amino, C_{1-4} alkyl, C_{1-4} halo alkyl and C_{3-4} cycloalkyl. In yet other embodiments, Y is substituted with up to four substituents selected from methyl, propyl, i-propyl, ethyl, hydroxyl, amino, halo, monohalo C_{1-3} alkyl, trihalo C_{1-3} alkyl and dihalo C_{1-3} alkyl.

[0012] In some embodiments, new compounds of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is selected from a group consisting of substituted or unsubstituted cyclohexyl, cyclohexynyl, and piperidinyl, wherein each member of said group is substituted with up to four substituents.

[0013] In some embodiments, new compounds of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is substituted with up to four substituents independently selected from hydrogen, cyano, nitro, halo, hydroxyl, amino, alkoxy, substituted amino, C_{1-4} alkyl, C_{1-4} halo alkyl and C_{3-4} cycloalkyl. In some embodiments, the substituents are independently selected from methyl, propyl, i-propyl, ethyl, hydroxyl, amino, halo, monohalo C_{1-3} alkyl, trihalo C_{1-3} alkyl and dihalo C_{1-3} alkyl.

[0014] In some embodiments, compounds of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_{12} is selected from hydrogen, halo, methyl, ethyl and cyano.

[0015] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is selected from the group consisting of substituted or unsubstituted cyclohexyl, cyclohexenyl, piperidinyl, piperazinyl, wherein said the Y group may be substituted with up to three substituents selected from methyl, ethyl, hydroxyl, amino, and methoxy; R_1 is selected from the group consisting of hydrogen, and amino; and R_{12} independently are each occurrence represents hydrogen, halo, or methyl.

[0016] In some embodiments, compounds of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided, wherein Y is selected from a group consisting of substituted cyclohexyl, cyclohexenyl, piperidinyl, and piperazinyl; R_1 is selected from the group consisting of hydrogen, $-NH_2$, halo, C_{1-4} alkyl, C_{3-4} cycloalkyl, and -CN; R_{12} independently at each occurrence is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and amino; and R_5 is selected from the group consisting of substituted or unsubstituted phenyl, cyclohexyl, cyclopentyl, thiazole, pyridyl, pyrimidyl and pyrazinyl, wherein the R_5 group may be substituted with up to three substituents selected from halo, hydrogen, methyl, substituted aminocarbonyl and alkoxy.

[0017] In a representative embodiment, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided, selected from the group consisting of N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-

yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, and N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, and 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide.

[0018] In other aspects, the present invention provides methods for treating Provirus Integration of Maloney Kinase (PIM Kinase) related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to inhibit PIM activity in the subject.

[0019] In other aspects, the present invention provides methods for treating PIM related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to reduce or prevent tumor growth in the subject.

[0020] In yet other aspects, the present invention provides methods for treating PIM related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer.

[0021] In yet other aspects, the present invention provides therapeutic compositions comprising at least one compound of Formula I or II in combination with one or more additional agents for the treatment of cancer, as are commonly employed in cancer therapy.

[0022] The compounds of the invention are useful in the treatment of cancers, including hematopoietic malignancies, carcinomas (e.g., of the lungs, liver, pancreas, ovaries, thyroid, bladder or colon), melanoma, myeloid disorders (e.g., myeloid leukemia, multiple myeloma and erythroleukemia), adenomas (e.g., villous colon adenoma), sarcomas (e.g., osteosarcoma), autoimmune diseases, allergic reactions and in organ transplantation rejection syndromes.

[0023] The invention further provides compositions, methods of use, and methods of manufacture as described in the detailed description of the invention.

DESCRIPTION OF THE DRAWINGS

[0024] The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

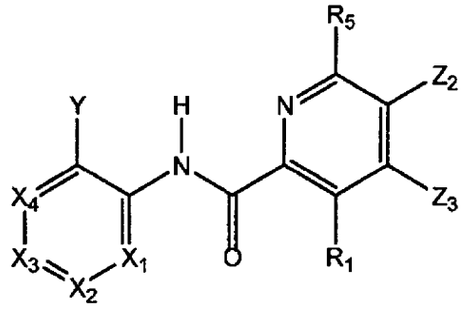
[0025] FIGURE 1 is a graph showing the efficacy of the compound of Example 99 from an evaluation in the KMS11-luc xenograft model, as described in Example 144.

[0026] FIGURE 2 is a graph showing the efficacy of the compound of Example 70 from an evaluation in the KMS11-luc xenograft model, as described in Example 144.

[0027] FIGURE 3 is a graph showing the efficacy of the compound of Example 96 from an evaluation in the KMS11-luc xenograft model, as described in Example 144.

DETAILED DESCRIPTION

[0028] In accordance with one aspect of the present invention, new compounds, and their stereoisomers, tautomers and pharmaceutically acceptable salts, are provided of the Formula I:



I

wherein,

X_1, X_2, X_3 and X_4 are independently selected from CR_2 and N; provided that at least one but not more than two of X_1, X_2, X_3 and X_4 are N;

Y is selected from a group consisting of cycloalkyl, partially unsaturated cycloalkyl, and heterocycloalkyl, wherein each member of said group may be substituted with up to four substituents;

Z_2 and Z_3 are independently selected from CR_{12} and N; provided that not more than one of Z_2 and Z_3 can be N;

R_1 is selected from the group consisting of hydrogen, $-NHR_3$, halo, hydroxyl, alkyl, cyano, and nitro;

R_2 and R_{12} independently at each occurrence are selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, SO_3H and substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, hetero cycloalkyl, and partially saturated cycloalkyl;

R_3 is selected from the group consisting of hydrogen, $-CO-R_4$ and substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_4 is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, and alkylamino; and

R_5 represents a group selected from substituted or unsubstituted aryl, C_3-C_7 cycloalkyl, heteroaryl, partially unsaturated cycloalkyl and alkyl, wherein each said substituted R_5 group may be substituted with up to four substituents selected from halo, cyano, amino, C_{1-4} alkyl, C_{3-6} cycloalkyl, alkoxy, nitro, carboxy, carbonyl, carboalkoxy, aminocarboxy, substituted aminocarbonyl, aminosulfonyl, substituted aminosulfonyl and alkoxyalkyl.

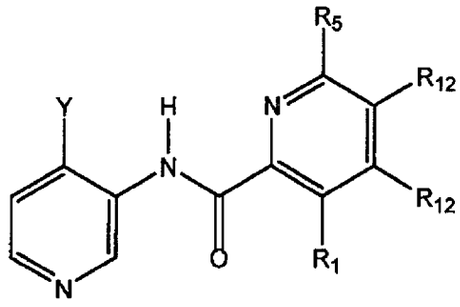
[0029] In some embodiments, new compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein X_2 is N and X_1, X_3 and X_4 are CR_2.

[0030] In some embodiments, new compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_2 is selected from hydrogen, methyl, ethyl, halo, cyano.

[0031] In some embodiments, compounds of formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Z_2 and Z_3 are CR_{12}.

[0032] In some embodiments, compounds of formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_{12} is selected from hydrogen, halo, methyl, ethyl and cyano.

[0033] In other embodiments, new compounds, and their stereoisomers, tautomers and pharmaceutically acceptable salts, are provided of the Formula II



II

wherein,

Y is selected from a group consisting of cyclohexyl, partially unsaturated cyclohexyl, and heterocyclo-C_5-alkyl, wherein each member of said group may be substituted with up to four substituents;

R_1 is selected from the group consisting of hydrogen, -NHR_3, halo, hydroxyl, alkyl, C_{3-4} cycloalkyl, cyano, and nitro;

R_{12} independently at each occurrence is selected from the group consisting of hydrogen, halo, hydroxyl, amino, nitro, cyano, SO_3H and substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, hetero cycloalkyl, and partially saturated cycloalkyl;

R_3 is selected from the group consisting of hydrogen, -CO-R_4 and substituted or unsubstituted alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R_4 is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, and alkylamino; and

R_5 is represents a group selected from hydrogen and substituted or unsubstituted alkyl, C_6-cycloalkyl, aryl and heteroaryl.

[0034] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is selected from a group consisting of substituted or unsubstituted cycloalkyl, cycloalkenyl, piperidinyl and piperazinyl, wherein each member of said group is substituted with up to four substituents. In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are

provided wherein Y is selected from a group consisting of substituted or unsubstituted cyclohexyl, cyclohexynyl, and piperidinyl, wherein each member of said group is substituted with up to four substituents. In some embodiments, Y is substituted with up to four substituents selected from hydrogen, cyano, nitro, halo, hydroxyl, amino, alkoxy, substituted amino, C_{1-4} alkyl, C_{1-4} halo alkyl and C_{3-4} cycloalkyl. In yet other embodiments, Y is substituted with up to four substituents selected from methyl, propyl, i-propyl, ethyl, hydroxyl, amino, halo, monohalo C_{1-3} alkyl, trihalo C_{1-3} alkyl and dihalo C_{1-3} alkyl.

[0035] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_1 is hydrogen, amino or fluoro. In one embodiment are provided compounds of Formula II selected from Table I or Table II.

[0036] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_5 is selected from substituted or unsubstituted aryl, C_5-C_6 cycloalkyl, heteroaryl, partially unsaturated C_5-C_6 cycloalkyl and C_1-C_4 alkyl, wherein each said group can be substituted with up to four substituents selected from halo, cyano, amino, C_{1-4} alkyl, C_{3-5} cycloalkyl, alkoxy, nitro, carboxy, carbonyl, carboalkoxy, aminocarboxy, substituted aminocarbonyl, aminosulfonyl, substituted aminosulfonyl and alkoxyalkyl. In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_5 is substituted or unsubstituted phenyl, wherein the phenyl group can be substituted with up to four substituents selected from hydrogen, cyano, nitro, halo, hydroxyl, amino, alkoxy, substituted amino, C_{1-4} alkyl, C_{1-4} halo alkyl and C_{3-4} cycloalkyl. In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_5 is 2,6-difluororphenyl.

[0037] In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein R_{12} is selected from hydrogen, halo, methyl, ethyl and cyano. In some embodiments, compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided wherein Y is selected from the group consisting of substituted or unsubstituted cyclohexyl, cyclohexenyl, piperidinyl, piperazinyl, wherein said the Y group may be substituted with up to three substituents selected from methyl,

ethyl, hydroxyl, amino, and methoxy; R_1 is selected from the group consisting of hydrogen, and amino; and R_{12} independently are each occurrence represents hydrogen, halo, or methyl.

[0038] In some embodiments, compounds of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are provided, wherein Y is selected from a group consisting of substituted cyclohexyl, cyclohexenyl, piperidinyl, and piperazinyl; R_1 is selected from the group consisting of hydrogen, $-NH_2$, halo, C_{1-4} alkyl, C_{3-4} cycloalkyl, and -CN; R_{12} independently at each occurrence is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and amino; and R_5 is selected from the group consisting of substituted or unsubstituted phenyl, cyclohexyl, cyclopentyl, thiazole, pyridyl, pyrimidyl and pyrazinyl, wherein the R_5 group may be substituted with up to three substituents selected from halo, hydrogen, methyl, substituted aminocarbonyl and alkoxy.

[0039] A preferred embodiment of the present invention is a compound of Formula (II), wherein Y is cyclohexyl, substituted with one to three substitutents, said substituents preferably selected from hydroxyl, amino, C_{1-4} alkyl or C_{1-4} halo alkyl, and more preferably, selected from methyl, hydroxyl, amino, and CF_3, and most preferably from methyl, amino, and hydroxy; R_1 is hydrogen, NH_2, or halo (preferably, R_1 is hydrogen, amino or fluoro, more preferably, R_1 is hydrogen); R_{12} are each independently hydrogen or halo (preferably, each R_{12} is hydrogen, chloro or fluoro); R_5 is cyclohexyl, phenyl, or pyridyl, wherein said cyclohexyl, said phenyl and said pyridyl are each independently substituted with up to three substituents selected form halo, hydroxyl, C_{1-4} alkyl, and C_{1-4} alkoxy (preferably, R_5 is pyridyl or phenyl each independently substituted with up to three substitutents selected form halo, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy, more preferably, R_5 is phenyl substituted with up to three substituents selected form halo, hydroxyl, C_{1-4} alkoxy and C_{1-4} alkyl, most preferably, phenyl substituted with up to three substitutents selected from fluoro, hydroxyl, methyl, ethyl, methoxy, or propoxy, most preferably, R_5 is 2,6-difluorophenyl.

[0038] Yet another preferred embodiment of the present invention provides a compound of Formula II, wherein Y is piperidinyl substituted with methyl, hydroxyl, and amino; R_1 is hydrogen, NH_2, or fluoro; R_{12} independently at each occurrence is selected from the group consisting of hydrogen, and halo; and R_5 is pyridyl, fluoro pyridyl, cyclohexyl, or phenyl, wherein said phenyl is substituted with up to three substituents

selected from fluoro, hydroxyl, and methyl, preferably R_5 being difluoro phenyl. In a further preferred embodiment preferably Y is 3-amino-4-hydroxy-5-methylpiperidin-1-yl; R_1 is hydrogen; and R_5 is 2,6-difluoro phenyl.

[0041] In a representative embodiment, preferred compounds of Formulas I or II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof are selected from the group consisting of N-(4-((3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide; N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide; 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl) pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide); N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3S)-3-aminocyclohexyl)-pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; and 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide.

[003942] In other aspects, the present invention provides methods for treating Provirus Integration of Maloney Kinase (PIM Kinase) related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to inhibit PIM activity in the subject.

A preferred embodiment of the present invention provides a method for treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I.

[0043] In other aspects, the present invention provides methods for treating PIM related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to reduce or prevent tumor growth in the subject. In yet other aspects, the present invention provides methods for treating PIM related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula I or II effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer.

[0044] In yet other aspect, the present invention provides therapeutic compositions comprising at least one compound of Formula I or II in combination with one or more additional agents for the treatment of cancer, as are commonly employed in cancer therapy. The present invention thus provides a pharmaceutical composition comprising a compound of Formula I or Formula II. A preferred embodiment of this aspect provides a pharmaceutical composition comprising a compound selected from N-(4-((3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide; N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl) pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide); N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((1R,3S)-3-aminocyclohexyl)-pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((3R,4R,5S)-3-

amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; and N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide. Another preferred embodiment provides a pharmaceutical composition further comprising an additional agent for the treatment of cancer, wherein preferably the additional agent is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, and trastuzumab.

[0040] The compounds of the invention are useful in the treatment of cancers, including hematopoietic malignancies, carcinomas (e.g., of the lungs, liver, pancreas, ovaries, thyroid, bladder or colon), melanoma, myeloid disorders (e.g., myeloid leukemia, multiple myeloma and erythroleukemia), adenomas (e.g., villous colon adenoma), sarcomas (e.g., osteosarcoma), autoimmune diseases, allergic reactions and in organ transplantation rejection syndromes.

[0046] In yet another aspect of the present invention is provided a use of a compound of Formula I or Formula II for preparing a medicament for treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity . In a preferred embodiment of this aspect of the invention the condition is a cancer selected from carcinoma of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma and erythro leukemia, villous colon adenoma, and osteosarcoma.

[0047] In another aspect, the present invention relates to methods of inhibiting the activity of at least one kinase selected from the group consisting of Pim1, Pim2 and Pim3, in a subject, or treating a biological condition mediated by at least one of Pim1, Pim2 and Pim3, in a human or animal subject in need of such treatment, comprising administering to the subject at least one compound of Formula I or II in an amount

effective to inhibit the kinase in the subject. The therapeutic compounds are useful for treating patients with a need for such inhibitors (e.g., those suffering from cancer mediated by abnormal serine/threonine kinase receptor signaling).

DEFINITIONS

[0048] "PIM inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to PIM Kinase activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the PIM depletion assays described hereinbelow.

[0049] The phrase "alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2$-$CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. Thus the phrase alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups having 1 to 12 carbon atoms. A preferred "alkyl" definition refers to C_{1-4} straight chain alkyl groups such as methyl, ethyl, n-propyl, and n-butyl. The preferred alkyl definiton also includes C_{3-5} branched alkyl groups, including $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $CH(CH_3)CH_2CH_2CH_3$, $CH(CH_3)CH(CH_3)_2$, $CH_2CH(CH_3)CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, and $CH(CH_2CH_3)_2$, etc.

[0050] The term "alkenyl" refers to alkyl groups as defined above, wherein there is at least one point of unsaturation, i.e., wherein two adjacent carbon atoms are attached by a double bond. The term "alkynyl" refers to alkyl groups wherein two adjacent carbon atoms are attached by a triple bond. The term 'alkoxy" refers to -OR, wherein R is alkyl.

[0041] As used herein, the term "halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups. "Haloalkyl" refers to an alkyl radical substituted with one or

more halogen atoms. The term "haloalkyl" thus includes monohalo alkyl, dihalo alkyl, trihalo alkyl and the like. Representative monohalo alkyl groups include -CH_2F, -CH_2Cl, -CH_2CH_2F, -CH_2CH_2Cl, -$CH(F)CH_3$, -$CH(Cl)CH_3$; representative dihalo alkyl groups include $CHCl_2$, -CHF_2, -CCl_2CH_3, -$CH(Cl)CH_2Cl$, -CH_2CHCl_2, -CH_2CHF_2; representative trihalo alkyl groups include -CCl_3, -CF_3, -CCl_2CH_2Cl, -CF_2CH_2F, -$CH(Cl)CHCl_2$, -$CH(F)CHF_2$; and representative perhalo alkyl groups include -CCl_3, -CF_3, -CCl_2CCl_3, -CF_2CF_3.

[0042] "Amino" refers herein to the group –NH_2. The term "alkylamino" refers herein to the group –NRR' where R and R' are each independently selected from hydrogen or a lower alkyl. The term "arylamino" refers herein to the group –NRR' where R is aryl and R' is hydrogen, a lower alkyl, or an aryl. The term "aralkylamino" refers herein to the group –NRR' where R is a lower aralkyl and R' is hydrogen, a loweralkyl, an aryl, or a loweraralkyl. The term cyano refers to the group –CN. The term nitro refers to the group –NO_2.

[0043] The term "alkoxyalkyl" refers to the group –alk_1-O-alk_2 where alk_1 is alkyl or alkenyl, and alk_2 is alkyl or alkenyl. The term "loweralkoxyalkyl" refers to an alkoxyalkyl where alk_1 is loweralkyl or loweralkenyl, and alk_2 is loweralkyl or loweralkenyl. The term "aryloxyalkyl" refers to the group –alkyl-O-aryl. The term "aralkoxyalkyl" refers to the group -alkylenyl-O-aralkyl, where aralkyl is a loweraralkyl.

[0044] The term "aminocarbonyl" refers herein to the group –C(O)-NH_2. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweralkyl and R' is hydrogen or a loweralkyl. In some embodiments, R and R', together with the N atom attached to them may be taken together to form a "heterocycloalkylcarbonyl" group. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is an aryl and R' is hydrogen, loweralkyl or aryl. "aralkylaminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweraralkyl and R' is hydrogen, loweralkyl, aryl, or loweraralkyl.

[0045] "Aminosulfonyl" refers herein to the group –$S(O)_2$-NH_2. "Substituted aminosulfonyl" refers herein to the group –$S(O)_2$-NRR' where R is loweralkyl and R' is hydrogen or a loweralkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group –aryl-$S(O)_2$–NH-aralkyl, where the aralkyl is loweraralkyl.

[0046] "Carbonyl" refers to the divalent group –C(O)-. "Carboxy" refers to–C(=O)–OH. "Alkoxycarbonyl" refers to ester –C(=O)–OR wherein R is alkyl.

"Loweralkoxycarbonyl" refers to ester –C(=O)–OR wherein R is loweralkyl. "Cycloalkyloxycarbonyl" refers to –C(=O)–OR wherein R is cycloalkyl.

[0047] "Cycloalkyl" refers to a mono- or polycyclic, carbocyclic alkyl substituent. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. Typical cycloalkyl substituents have from 3 to 8 backbone (i.e., ring) atoms in which each backbone atom is either carbon or a heteroatom. The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 4 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl moieties include, for example, morpholino, piperazinyl, piperidinyl and the like. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures. The term "partially unsaturated cycloalkyl", "partially saturated cycloalkyl", and "cycloalkenyl" all refer to a cycloalkyl group wherein there is at least one point of unsaturation, i.e., wherein to adjacent ring atoms are connected by a double bond or a triple bond. Illustrative examples include cyclohexynyl, cyclohexynyl, cyclopropenyl, cyclobutynyl, and the like.

[0048] The terms "substituted heterocycle", "heterocyclic group" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms may be optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above. The term or "heterocycloalkyl" as used herein refers to a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur, wherein the ring has no double bonds. For example, the term heterocyclo-C_5-alkyl refers to a 6-membered ring containing 5 carbon atoms and a heteroatom, such as N. The term "heterocycle" thus includes rings in which nitrogen is the heteroatom as well as partially and fully-saturated rings. Preferred heterocycles include, for example: diazapinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl,

pyrazolidinyl, imidazoyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl and benzothienyl.

[0049] Heterocyclic moieties can be unsubstituted or monosubstituted or disubstituted or trisubstituted with various substituents independently selected from hydroxy, halo, oxo (C=O), alkylimino (RN=, wherein R is a loweralkyl or loweralkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, loweralkyl, cycloalkyl or haloalkyl.

[0050] The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

[0051] Representative heterocyclics include, for example, imidazolyl, pyridyl, piperazinyl, piperidinyl, azetidinyl, thiazolyl, furanyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, naphthpyridinyl, indazolyl, and quinolizinyl.

[0052] "Aryl" refers to optionally substituted monocyclic and polycyclic aromatic groups having from 3 to 14 backbone carbon or hetero atoms, and includes both carbocyclic aryl groups and heterocyclic aryl groups. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon. The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example, benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, i.e., , naphthyl, and the like. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

[0053] "Optionally substituted" or "substituted" refers to the replacement of one or more hydrogen atoms with a monovalent or divalent radical. Suitable substitution groups include, for example, hydroxy, nitro, amino, imino, cyano, halo, thio, sulfonyl,

thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkylamino, halologweralkylamino, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like.

[0054] The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo; nitro, amino, cyano, hydroxy, loweralkyl, loweralkoxy, aminocarbonyl, -SR, thioamido, $-SO_3H$, $-SO_2R$ or cycloalkyl, where R is typically hydrogen, hydroxyl or loweralkyl.

[0055] When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms. It is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with five fluoro groups or a halogen atom substituted with another halogen atom). Such impermissible substitution patterns are well known to the skilled artisan.

[0056] It will also be apparent to those skilled in the art that the compounds of the invention, or their stereoisomers, as well as the pharmaceutically acceptable salts, esters, metabolites and prodrugs of any of them, may be subject to tautomerization and may therefore exist in various tautomeric forms wherein a proton of one atom of a molecule shifts to another atom and the chemical bonds between the atoms of the molecules are consequently rearranged. See, e.g., March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). As used herein, the term "tautomer" refers to the compounds produced by the proton shift, and it should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention.

[0057] The compounds of the invention, or their tautomers, as well as the pharmaceutically acceptable salts, esters, metabolites and prodrugs of any of them, may comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention existing in enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, such as in (R)- or (S)- forms. As a result, all such possible isomers,

individual stereoisomers in their optically pure forms, mixtures thereof, racemic mixtures (or "racemates"), mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure Appl. Chem.* *45*:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

[0058] As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of Formula I or II. These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formula I or II, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0059] Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid,

methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

[0060] As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

[0061] The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference

[0062] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0073] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium

incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0074] Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

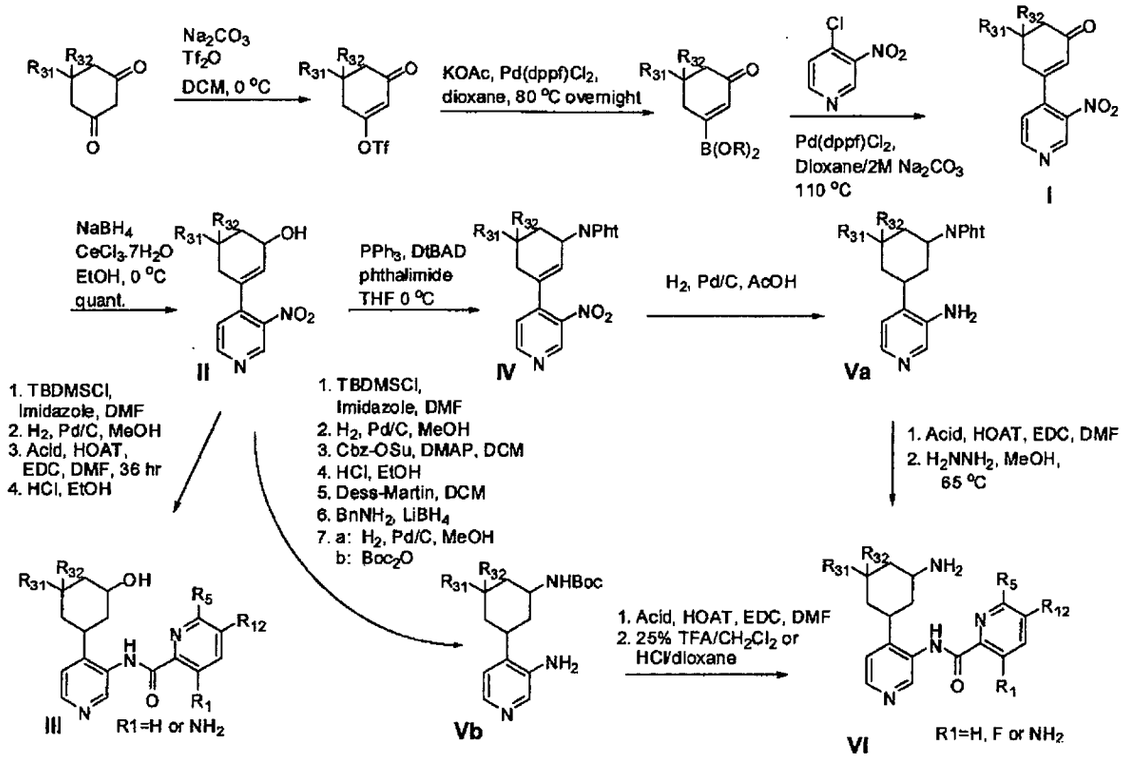
[0075] It will be apparent to those skilled in the art that the compounds of the invention, or their tautomers, prodrugs and stereoisomers, as well as the pharmaceutically acceptable salts, esters and prodrugs of any of them, may be processed *in vivo* through metabolism in a human or animal body or cell to produce metabolites. The term "metabolite" as used herein refers to the formula of any derivative produced in a subject after administration of a parent compound. The derivatives may be produced from the parent compound by various biochemical transformations in the subject such as, for example, oxidation, reduction, hydrolysis, or conjugation and include, for example, oxides and demethylated derivatives. The metabolites of a compound of the invention may be identified using routine techniques known in the art. See, e.g., Bertolini, G. et al., *J. Med. Chem. 40*:2011-2016 (1997); Shan, D. et al., *J. Pharm. Sci. 86*(7):765-767; Bagshawe K., *Drug Dev. Res. 34*:220-230 (1995); Bodor, N., *Advances in Drug Res. 13*:224-331 (1984); Bundgaard, H., *Design of Prodrugs* (Elsevier Press 1985); and Larsen, I. K., *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991). It should be understood that individual chemical compounds that are metabolites of the compounds of formula I, formula II, or their tautomers, prodrugs and stereoisomers, as well as the pharmaceutically acceptable salts, esters and prodrugs of any of them, are included within the invention.

[0076] The term "cancer" refers to cancer diseases that can be beneficially treated by the inhibition of Pim kinase, including, for example, solid cancers, such as carcinomas (e.g., of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon), melanomas, myeloid disorders (e.g., myeloid leukemia, multiple myeloma and erythroleukemia), adenomas (e.g., villous colon adenoma) and sarcomas (e.g., osteosarcoma).

SYNTHETIC METHODS

[0077] The compounds of the invention can be obtained through procedures known to the skilled in the art. For example, as shown in Scheme 1, cyclohexanediones can be converted via monotriflates to the corresponding cyclohexenoneboronate esters which can undergo palladium mediated carbon bond formation with 4-chloro, 3-nitro pyridine to yield nitropyridine substituted cyclohexenones I. Reduction of the enone functionality can yield a cyclohexenol II which upon alcohol protection, nitro and alkene reduction, amide coupling and deprotection can yield cyclohexanol amides III. Cyclohexenol II can also undergo Mitsunobu reaction with phthalimide to yield a protected aminocyclohexene IV. Following nitro and alkene reduction, phthalimide protected aminocyclohexyl pyridyl aniline Va can undergo amide coupling and deprotection, to yield aminocyclohexane amides VI. The corresponding Boc protected aminocyclohexane pyridyl aniline Vb can also be prepared from cyclohexenol II in the following manner: alcohol protection, alkene and nitro reduction, pyridyl amine Cbz protection, silyl ether deprotection, Dess-Martin oxidation to the cyclohexanone, reductive amination with benzylamine, Cbz and Bn deprotection and primary aliphatic amine Boc protection. In the amide products III and VI, if R_2 is halo or triflate, the amides III and VI can be further modified by standard modifications to introduce substituted aryls, alkyls and heteroaryls at R_2. For example, if R_2 is Br, by reaction with boronic acids or organometallic reagents, or conversion to the corresponding boronate ester and reaction with aryl/heteroaryl halides or triflates, a variety of R_2 modifications are possible.

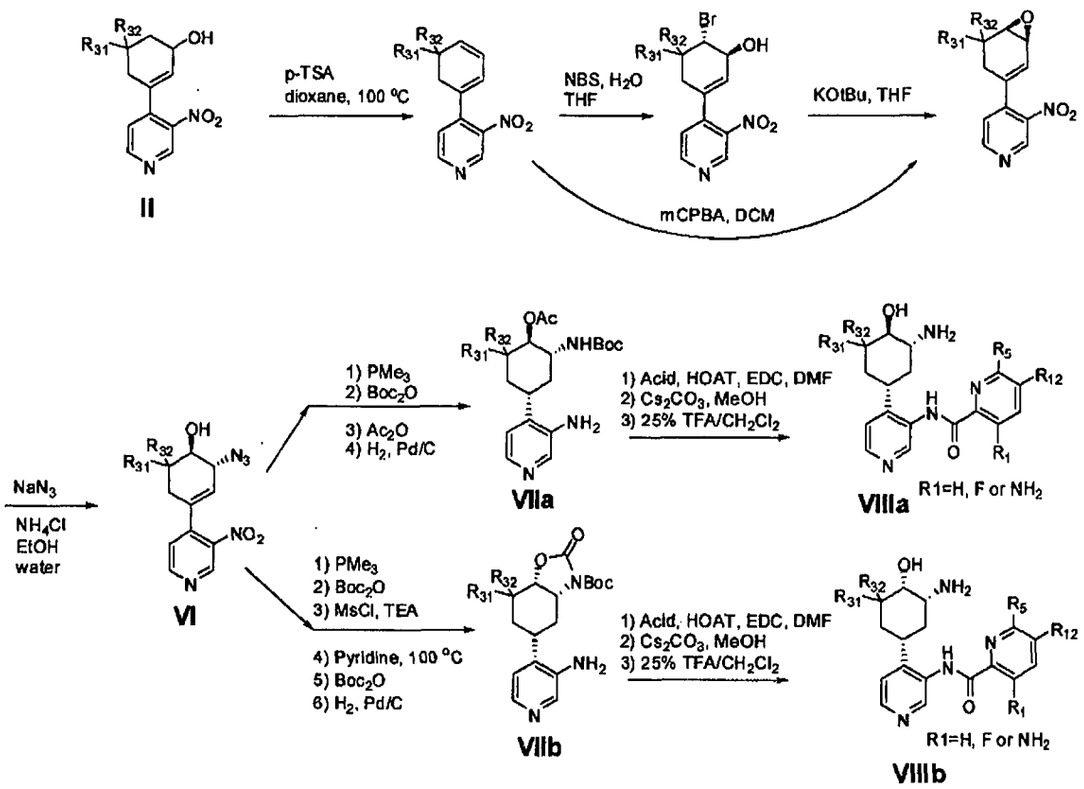
Scheme 1.



[0078] Alternatively, as shown in Scheme 2, cyclohexenol II can be dehydrated yielding a cyclohexadiene which upon epoxidation (via bromohydrin formation and HBr elimination or from mCPBA directly) and azide epoxide opening yields cyclohexenyl azido alcohol VI. Cyclohexenyl azido alcohol VI can be converted to the trans protected amino hydroxy aniline VIIa by azide reduction, alcohol protection and alkene and nitro reduction. Alternatively, the cyclohexenyl azido alcohol VI can be converted to the protected cis amino hydroxy aniline VIIb by azide reduction and Boc protection, alcohol mesylation and intramolecular cyclization to the cis cyclic carbamate, followed by Boc protection and alkene and nitro reduction. The resulting cyclohexylpyridyl anilines VIIa and VIIb can be converted to the corresponding pyridine amides VIIIa and VIIIb by amide coupling, acetate or cyclic carbamate cleavage and Boc deprotection. If R_2 is halo or triflate, the amides VIIIa and VIIIb can be further modified by standard modifications to introduce substituted aryls, alkyls and heteroaryls at R_2 after amide bond formation and prior to full deprotection. For example, if R_2 is Br, by reaction with boronic acids or organometallic reagents, or conversion to the

corresponding boronate ester and reaction with aryl/heteroaryl halides or triflates, a variety of R_2 modifications are possible.

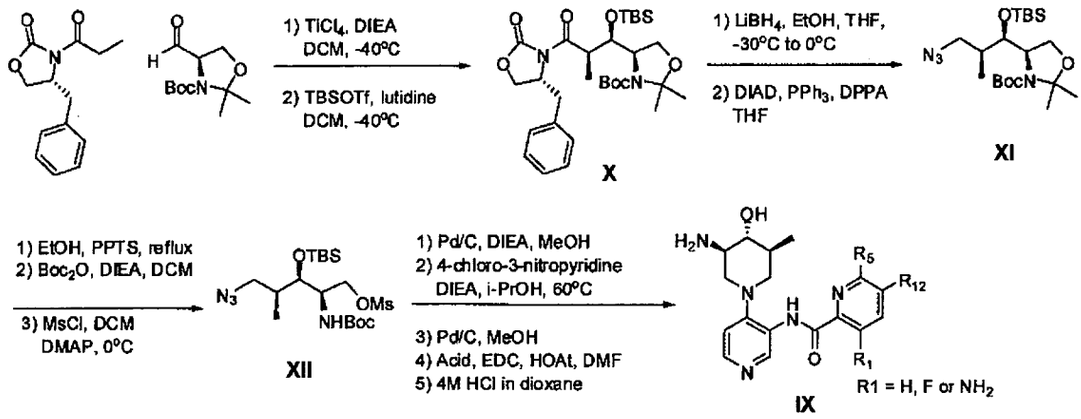
Scheme 2.



[0079] Alternatively, as shown in Scheme 3, trisubstituted 5-alkyl, 4-hydroxy, 3-aminopiperidines can be prepared and modified to yield trisubstituted 5-alkyl, 4-hydroxy, 3-aminopiperidinyl pyridine amides IX as follows. Reaction of Garner's aldehyde with (R)-4-benzyl-3-propionyloxazolidin-2-one followed by TBS protection of the resulting alcohol affords compound X. Reduction of the oxazolidinone followed by introduction of the azide group yields intermediate XI. Deprotection under acidic conditions reveals the corresponding amino alcohol, which upon protection with the Boc group followed by mesylation of the primary alcohol yields intermediate XII. Reduction of the azide affords formation of the piperidine which is subsequently reacted with 4-chloro-3-nitropyridine, reduced to the amine, coupled with the corresponding carboxylic acid and deprotected to provide trisubstituted 5-methyl,4-hydroxy-3-

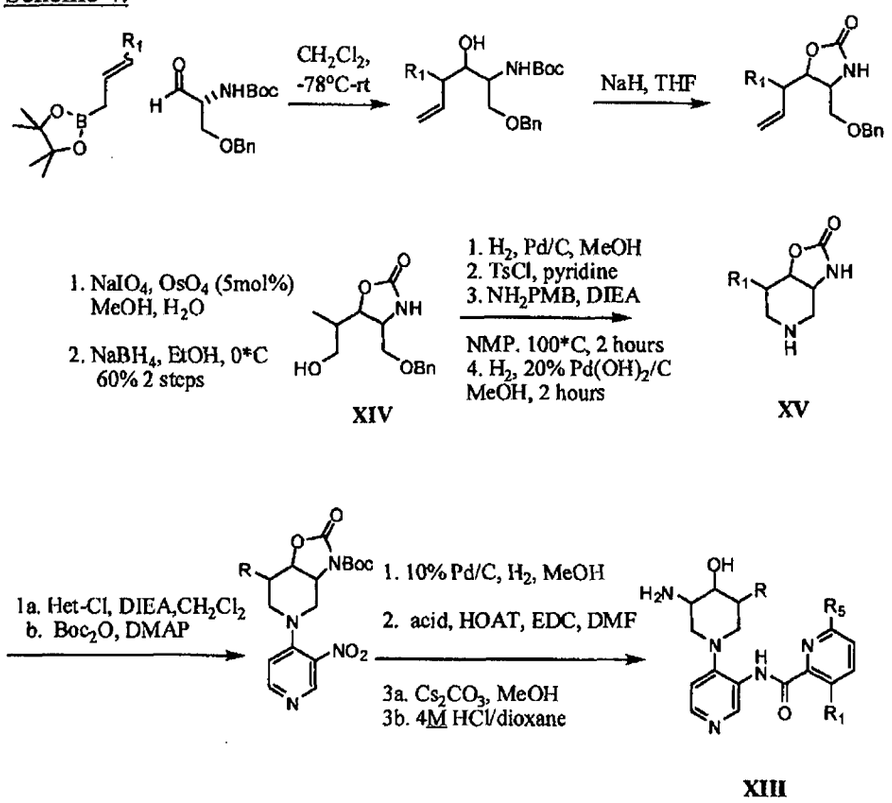
aminopiperidinyl pyridine amides IX. If R_1 is halo or triflate, the amide IX can be further modified by standard modifications to introduce substituted aryls, alkyls and heteroaryls at R_1 after amide bond formation and prior to full deprotection. For example, if R_1 is Br, by reaction with boronic acids or organometallic reagents, or conversion to the corresponding boronate ester and reaction with aryl/heteroaryl halides or triflates, a variety of R_1 modifications are possible.

Scheme 3.



[0080] Alternatively, as shown in Scheme 4, trisubstituted 5-methyl, 4-hydroxy, 3-aminopiperidines can also be prepared and modified to yield trisubstituted 5-methyl, 4-hydroxy, 3-aminopiperidinyl amides XIII as follows. Reaction of crotyl boronate esters with SerOBn aldehyde followed by cyclic carbamate formation, alkene oxidative cleavage and reduction yields hydroxyl compound XIV. Benzyl deprotection followed by bistosylation and reaction with p-methoxybenzylamine, and amine deprotection yields piperidine XV. Reaction of substituted piperidine XV with halo nitro substituted arenes or heteroarenes followed by carbamate protection, nitro reduction, amide coupling, cyclic carbamate opening and deprotection yields trisubstituted 5-methyl, 4-hydroxy, 3-aminopiperidinyl amides XIII. If R_3 is halo or triflate, the amide XV can be further modified by standard modifications to introduce substituted aryls, alkyls and heteroaryls at R_3. For example, if R_3 is Br, by reaction with boronic acids or organometallic reagents, or conversion to the corresponding boronate ester and reaction with aryl/heteroaryl halides or triflates, a variety of R_3 modifications are possible.

Scheme 4.



[0081] The compounds of the invention are useful *in vitro* and/or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), incorporated herein by reference.

[0082] Effective amounts of the compounds of the invention generally include any amount sufficient to detectably inhibit Pim activity by any of the assays described herein, by other Pim kinase activity assays known to those having ordinary skill in the art or by detecting an inhibition or alleviation of symptoms of cancer. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage

form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0083] For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

[0084] The compounds of the present invention may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

[0085] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0086] Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and

polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

[0087] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

[0088] The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq.* (1976).

[0063] While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment of cancer. The compounds of the present invention are also useful in combination with known therapeutic agents and anti-cancer agents, and combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology*, V. T. Devita and S. Hellman (editors), 6th edition (Feb. 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. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The compounds of the invention are also useful when co-administered with radiation therapy.

[0064] Therefore, in one embodiment of the invention, the compounds of the invention are also used in combination with known anticancer agents including, for example, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

[0065] In certain presently preferred embodiments of the invention, representative agents useful in combination with the compounds of the invention for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, as well as other cancer chemotherapeutic agents.

[0066] The above compounds to be employed in combination with the compounds of the invention will be used in therapeutic amounts as indicated in the *Physicians' Desk Reference (PDR)* 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

[0067] The compounds of the invention and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate

compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

[0068] In one embodiment, the invention provides a method of inhibiting Pim1, Pim2 or Pim3 in a human or animal subject. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Formula I or II to a subject in need thereof.

[0069] The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0070] Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

[0071] The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 μ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

[0072] In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well-known iodine vapor and other various staining techniques.

[0073] Mass spectrometric analysis was performed on one of three LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 4 min period; flow rate 0.8 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature

40°C), another Waters System (ACQUITY UPLC system and a ZQ 2000 system; Column: ACQUITY UPLC HSS-C18, 1.8um, 2.1 x 50mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 1.3 min period; flow rate 1.2 mL/min; molecular weight range 150-850; cone Voltage 20 V; column temperature 50°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% acetonitrile in water with 0.05% TFA over a 4 min period; flow rate 0.8 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

[0074] Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 400 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent.

[0075] Preparative separations are carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography are dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

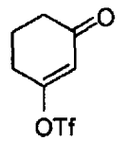
[0076] It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

[0077] It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

[0078] The examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

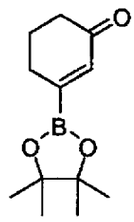
	ABBREVIATIONS
DAST	(diethylamino)sulfurtrifluoride
DCM	Dichloromethane
DIEA	diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	Ethanol
HOAT	Hydroxyazabenzotriazole
K_2CO_3	Potassium carbonate
MeCN	Acetonitrile
$MgSO_4$	Magnesium sulfate
MeOH	Methanol
Na_2CO_3	sodium carbonate
NaCl	Sodium chloride
$NaHCO_3$	sodium bicarbonate
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphospine)palladium(0)
$Pd(dppf)Cl_2$-DCM	Dichloro-(1,2-bis(diphenylphosphino)ethan)-Palladium(II) – dichloromothethane adduct
RT or rt	room temperature
TBDMSCl	tert-butyldimethylsilylchloride
TEA	Triethylamine
THF	tetrahydrofuran

Synthesis of 3-oxocyclohex-1-enyl trifluoromethanesulfonate



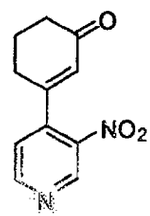
[0079] To a solution of cyclohexane-1,3-dione (1 equiv) in DCM (0.4 M) was added Na_2CO_3 (1.0 equiv.) and cooled to 0 °C. Added Tf_2O (1.0 equiv.) in DCM (5 M) dropwise over 1 hr at room temperature under a nitrogen atmosphere. Upon addition, the reaction was stirred for 2 hr (dark red solution). The solution was filtered and to the filtrate was added saturated $NaHCO_3$ (carefully), then extracted the organics, dried with brine, then Na_2SO_4, and concentrated. The crude was used for the next step without further purification. 3-oxocyclohex-1-enyl trifluoromethanesulfonate was obtained in 67% yield. The triflate decomposes upon storage and should be used immediately for the next reaction. LC/MS=244.9/286.0 (M+H and M+CH_3CN); Rt = 0.88 min.

Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone



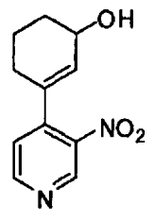
[0080] To a solution of 3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 equiv.) in degassed dioxane (0.3 M) was added bis(pinacolato)diboron (2.0 equiv.), KOAc (3.0 equiv.), and Pd(dppf)Cl_2-DCM (0.05 equiv.). The reaction was heated to 80 °C for 2 h, then filtered. The dioxane solution was used for the next step without further purification. LC/MS = 140.9 (M+H of boronic acid).

Synthesis of 3-(3-nitropyridin-4-yl)cyclohex-2-enone



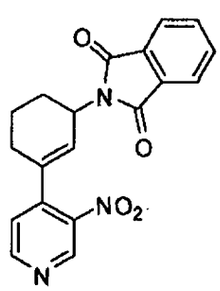
[0081] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (1.0 equiv.) in degassed dioxane and 2M Na_2CO_3 was added 4-chloro-3-nitropyridine (1.2 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.). The reaction was heated in an oil bath to 110 °C for 2 hours. Cooled to room temperature, then diluted with EtOAc, added H_2O – dark solution, lots of emulsions. Filtered to get rid of the solids, then extracted the organic phase, dried with Na_2SO_4, and concentrated. The crude was purified via silica gel chromatography eluting with ethyl acetate and hexanes (1:1) to yield 3-(3-nitropyridin-4-yl)cyclohex-2-enone (55%, 2 steps). LC/MS = 219 (M+H), LC = 2.294 min.

Synthesis of 3-(3-nitropyridin-4-yl)cyclohex-2-enol



[0082] To a solution of 3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 equiv.) was added EtOH (0.2 M) and $CeCl_3$-$7H_2O$ (1.3 equiv.). The reaction was cooled to 0 °C, then $NaBH_4$ (1.3 equiv.) was added in portions. Stirred for 2 h at 0 °C, then quenched by adding water, concentrated to remove the EtOH, added EtOAc, extracted the organics, dried with brine, then Na_2SO_4, and concentrated to yield 3-(3-nitropyridin-4-yl)cyclohex-2-enol (99%). LC/MS = 221.1 (M+H), LC = 2.235 min.

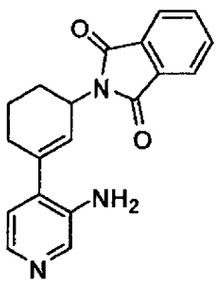
Synthesis of 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione



[0083] To a solution of 3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.), triphenylphosphine (1.5 equiv.) and phthalimide (1.5 equiv.) in THF (0.3 M) at 0 °C was

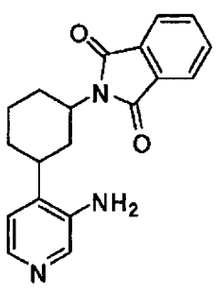
added (E)-di-tert-butyl diazene-1,2-dicarboxylate (1.5 equiv.) dropwise. The reaction was stirred at 0 °C for 2 hours. Concentrated to dryness under vacuo, then purified the crude via silica gel column chromatography eluting with EtOAc and hexanes (1:1 with 5% methanol) to afford the 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione (63% yield). LC/MS = 350.3 (M+H), LC = 3.936 min.

Synthesis of 2-(3-(3-aminopyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione



[0084] To a solution of 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione (1.0 equiv.) in AcOH (0.38 M) was added Fe (6.0 equiv.) and the reaction was stirred at room temperature for 2 h. Filtered, then washed with methanol and concentrated the filtrate. To the crude was added ethyl acetate and saturated $NaHCO_3$, the organics were dried with Na_2SO_4, and concentrated to give 2-(3-(3-aminopyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione as a yellow thick gum in 96% yield. LC/MS = 320.0 (M+H), LC = 2.410 min.

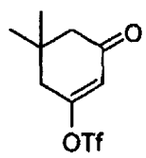
Synthesis of 2-(3-(3-aminopyridin-4-yl)cyclohexyl)isoindoline-1,3-dione



[0085] To a solution of 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione (1.0 equiv.) in acetic acid (0.1 M) was added 10% Pd/C (0.2 equiv.) and the reaction was stirred under a H_2 balloon. After 3 days, the reaction was filtered through Celite, washed with ethyl acetate and methanol, the filtrate was diluted with ethyl acetate

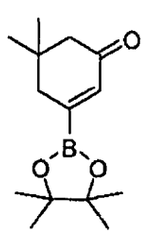
and washed twice with sat. 2M Na_2CO_3. The organic phase was dried with magnesium sulfate, filtered and concentrated. The crude material was triturated with hexanes and ethyl acetate to afford 2-(3-(3-aminopyridin-4-yl)cyclohexyl)isoindoline-1,3-dione in 73% yield. LC/MS = 322.2 (M+H), Rt = 0.64 min.

Synthesis of 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate



[0086] In a 3-neck round-bottom flask, 5,5-dimethylcyclohexane-1,3-dione (1.0 eq) was dissolved in DCM (0.2 M). Sodium carbonate (1.1 eq) was added and the mixture was cooled with magnetic stirring on an ice/salt water bath to ~ -5 °C under N_2. Triflic anhydride (1.05 equiv.) diluted in DCM was added dropwise via addition funnel over 90 minutes. Upon completion of addition, the reaction was stirred at ~ 0 °C for 1h. From LCMS and 1H NMR, there was still starting material left. Additional sodium carbonate (0.51 eq) and triflic anhydride (0.50 eq) were added. After 2 hours, the mixture was filtered through a coarse frit glass funnel (the cake was washed with DCM), transferred to an Erlenmeyer flask, quenched by careful addition of saturated aqueous sodium bicarbonate with vigorous stirring until pH =7, transferred to a separatory funnel and the layers separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoro-methanesulfonate, which was used to the next step without further purification. LC/MS (*m/z*): MH^+=273.1, Rt=1.03.

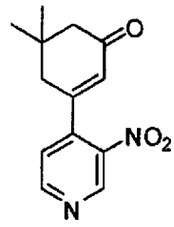
Synthesis of 5,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone



[0087] All of reagents 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoro-methanesulfonate (1.0 eq), potassium acetate (3.0 eq), and bis(pinacolato)diboron (2.0 eq)

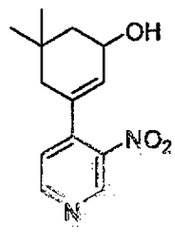
were added to 1,4-dioxane (0.2 M) in a round bottomed flask and degassed by bubbling N_2 through the mixture for 10 min. $PdCl_2$(dppf) - DCM adduct (0.03 eq) was added and the reaction heated to 80 °C fitted with a reflux condenser on an oil bath under N_2 overnight. The mixture was cooled to room temperature, filtered through a coarse frit glass funnel, the cake rinsed with 1,4-dioxane to give the 5,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone in 1,4-dioxane which was used to next step without further purification. LC/MS (*m/z*): MH^+(boronic acid) =169.1, Rt=0.50.

Synthesis of 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone



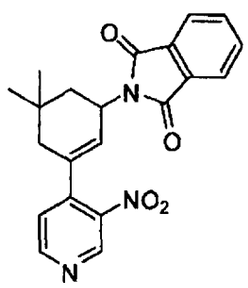
[0088] The boronate ester 5,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (1.0 eq) was dissolved in 1,4-dioxane in a round bottomed flask and degassed by bubbling N_2 through the solution for 30 minutes. 4-chloro-3-nitro-pyridine (1.3 eq) and 2M(aq) sodium carbonate (2.0 eq) were added and N_2 was bubbled through for 10 minutes and then $PdCl_2$(dppf) - DCM (0.05 eq) was added. The reaction mixture was stirred at 110 °C for 2 hr. The mixture was added to EtOAc and water. The resulting mixture was filtered through celite, the cake was washed with EtOAc. The organic layer was separated and the aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (eluted with EtOAc:Hexanes = 1:10 to 2:1) to give 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (46.7% for three steps). LC/MS (*m/z*): MH^+=247.2, Rt=0.79.

Synthesis of 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



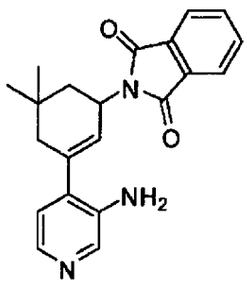
[0089] To a solution of 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 eq), and $CeCl_3$-$7H_2O$ (1.2 eq) in MeOH (0.2 M) was added $NaBH_4$ (1.0 eq) at 0 °C. The solution was stirred for 1 hour, and then quenched by the addition of 5 mL of water. The volatiles were removed in vacuum and the residue was partitioned between EtOAc and H_2O. The organic layer was separated and washed with brine. The combined aqueous was back extracted with EtOAc and the organic was washed with brine. The combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (74%). LC/MS (*m/z*): MH^+=249.2, Rt=0.76.

Synthesis of 2-(5,5-dimethyl-3-(3-nitropyridin-4-yl)- cyclohex-2-enyl)isoindoline-1,3-dione



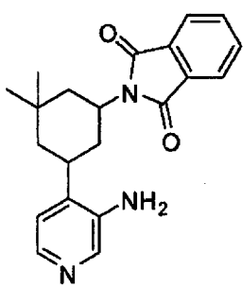
[0090] To a homogeneous solution of 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 eq), triphenyl phosphine (1.5 eq), and phthalimide (1.5 eq) in THF (0.2 M) cooled to 0 °C, ditertbutyl azodicarboxylate (1.5 eq) in THF was added to the solution. The mixture was stirred at 0 °C for 2 hours. The reaction was concentrated *in vacuo*. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 2-(5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione (99%). LC/MS (*m/z*): MH^+=378.2, Rt=1.10.

Synthesis of 2-(3-(3-aminopyridin-4-yl)-5,5-dimethyl-cyclohex-2-enyl)isoindoline-1,3-dione



[0091] A solution of 2-(5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione (1 eq) in acetic acid (0.1 M) was purged with nitrogen for 10 min. Then 10% Pd/C (0.10 eq) was added. The reaction mixture was stirred at room temperature overnight under an atmosphere of hydrogen. Solids were removed by filtration over celite, then rinsed with EtOAc and MeOH. The filtrate was concentrated, diluted with EtOAc and washed 2x with sat. aq. 2M Na_2CO_3. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 2-(3-(3-aminopyridin-4-yl)-5,5-dimethylcyclohex-2-enyl)isoindoline-1,3-dione (89%). LC/MS (*m/z*): MH^+=348.3, Rt=0.79.

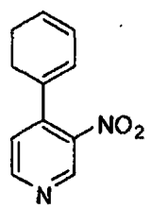
Synthesis of 2-(5-(3-aminopyridin-4-yl)-3,3-dimethylcyclohexyl)isoindoline-1,3-dione



[0092] A solution of 2-(3-(3-aminopyridin-4-yl)-5,5-dimethylcyclohex-2-enyl)isoindoline-1,3-dione (1.0 eq) in acetic acid (0.1 M) was purged with nitrogen for 10 min. Then 10% Pd/C (0.1 eq) was added. The reaction mixture was stirred at 45 °C, 300 psi hydrogen atmosphere in a steel bomb overnight and at 65 °C, 300 psi for 5 hours. Solids were removed by filtration over celite, then rinsed with EtOAc and MeOH. The filtrate was concentrated, diluted with EtOAc and washed 2x with sat. aq. 2M Na_2CO_3. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was

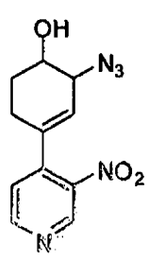
purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 2-(5-(3-aminopyridin-4-yl)-3,3-dimethylcyclohexyl)isoindoline-1,3-dione (53%). LC/MS (*m/z*): MH^+=350.3, Rt=0.78. The enantiomerically pure 2-((1*R*,5*R*)-5-(3-aminopyridin-4-yl)-3,3-dimethylcyclohexyl)isoindoline-1,3-dione and 2-((1*S*,5*S*)-5-(3-aminopyridin-4-yl)-3,3-dimethylcyclohexyl)isoindoline-1,3-dione were resolved by chiral HPLC (For analysis R_t = 7.526 min and 13.105 min respectively; hexanes:ethanol= 80:20 (v:v), Chiralcel OJ-H 100 x 4.6 mm at 1 mL/min. For preparative separation, hexanes:ethanol = 80:20 (v:v), Chiralcel OJ-H (250 x 20 mm at 20 mL/min). ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H), 8.00 (d, 1H), 7.82 (m, 2H), 7.71 (m, 2H), 7.06 (d, 1H), 4.54 (m, 1H), 3.71 (m, 2H), 2.89 (m, 1H), 2.23-2.44 (m, 2H), 1.90 (m, 1H), 1.20-1.60 (m, 3H), 1.18 (s, 3H), 1.07 (s, 3H).

Synthesis of 4-(cyclohexa-1,3-dienyl)-3-nitropyridine



[0093] To a solution of 3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) was added dioxane (0.18 M) and p-TSA (1.1 equiv.). The solution was heated to 100 °C for 4 h. Cooled to room temperature, worked up with sat. $NaHCO_3$ and ethyl acetate, the organic phase was dried with Na_2SO_4 and concentrated. The crude was purified via silica gel column chromatography eluting with 100% DCM to give 4-(cyclohexa-1,3-dienyl)-3-nitropyridine as a yellow oil (27% yield). LCMS (*m/z*): 203.1 (MH^+), LC R_t = 3.53 min, ^{1}H-NMR ($CDCl_3$): 9.02 (s, 1H), 8.70 (d, J=5.3, 1H), 7.30 (d, J=5.3, 1H), 6.15-6.17 (m, 1H), 6.02-6.11 (m, 2H), 2.35-2.38 (m, 4H).

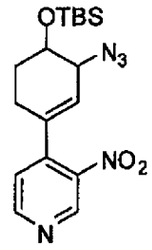
Synthesis of (+/-)-2-azido-4-(3-nitropyridin-4-yl)cyclohex-3-enol



[0094] To a solution of 4-(cyclohexa-1,3-dienyl)-3-nitropyridine (1.0 equiv.) in DCM (0.1 M) was added $NaHCO_3$ (1.2 equiv.) to give a yellow solution. Cooled to 0 °C, then added m-CPBA (1.0 equiv.) to the solution at once as a solid. The reaction was stirred at 0 °C for 3.5 hr. Monitored by both TLC and LC/MS. The product ionizes as M+H = 237 (diol); Rt=0.41min on UPLC. Quenched reaction with sat. $NaHCO_3$, then extracted with DCM (3 times). The organic phase was further dried with brine, then Na_2SO_4, filtered and concentrated to give the crude epoxide as a yellow oil, which was used without further purification.

[0095] To a solution of the above crude material in EtOH and water (3:1) (cloudy yellow solution) was added NaN_3 (2.0 equiv.) and NH_4Cl (2.0 equiv.) to give a clear orange solution. The reaction was stirred for 16 h, then concentrated. EtOAc and water were added, the organic phase was further dried with $MgSO_4$ and concentrated to give a brown oil. The oil was loaded in silica gel and purified via column chromatography (ISCO, 0-50% EtOAc) to give (+/-)-2-azido-4-(3-nitropyridin-4-yl)cyclohex-3-enol as a yellow oil (44% for 2 steps). LCMS (*m/z*) = 262 (MH^+), LC R_t = 2.35 min.

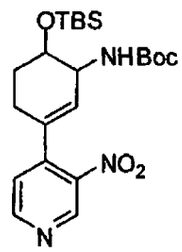
Synthesis of (+/-)-4-(3-azido-4-(tert-butyldimethylsilyloxy)cyclohex-1-enyl)-3-nitropyridine



[0096] To a solution of (+/-)-2-azido-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in DCM (0.15 M) was added TBSCl (2.0 equiv.), imidazole (2.0 equiv.) and DMAP (0.1 equiv.) at room temperature. After 18 h, water was added, the organics were dried with brine, then Na_2SO_4, and concentrated. The crude material was loaded to silica gel and purified via column chromatography (ISCO) eluting with ethyl acetate and hexanes (20%). Obtained (+/-)-4-(3-azido-4-(tert-butyldimethylsilyloxy)cyclohex-1-

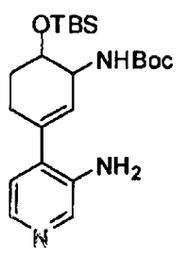
enyl)-3-nitropyridine as a yellow oil in 60% yield. LCMS (*m/z*): 376.3 (MH^+), LC R_t =5.848 min.

Synthesis of (+/-)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



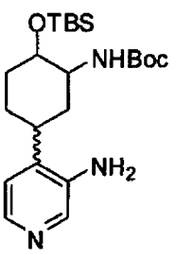
[0097] In a round-bottomed flask was added (+/-)-4-(3-azido-4-(tert-butyldimethylsilyloxy)cyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) and pyridine (0.1 M) to give a yellow solution. Ammonium hydroxide (10:1 pyridine: ammonium hydroxide) was added followed by PMe_3 (3.0 equiv.). The reaction turned dark brown after 10 min. Stirred at room temperature for 1.5 h. Quenched by adding EtOH, and concentrated. Repeated 2 more times. To the crude was added sat. $NaHCO_3$ and dioxane (1:1, 0.1M). Boc_2O (1.0 equiv.) was added. Stirred for one hour at room temperature. Washed with H_2O and EtOAc, the organic phase was dried with $MgSO_4$, filtered and concentrated. The residue was purified via silica gel column chromatography (ISCO, 5:1 Hex/EtOAc). Collected the pure fractions and concentrated to give (+/-)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate as a foam. LCMS (*m/z*): 450.3 (MH^+), LC R_t = 5.83 min.

Synthesis of (+/-)-tert-butyl 3-(3-aminopyridin-4-yl)-6-(tert-butyldimethylsilyloxy) cyclohex-2-enylcarbamate



[0098] To a solution of (+/-)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in AcOH (0.18 M) was added Fe (6.0 equiv.) and the reaction was stirred for 20 h. Worked up by diluting the reaction with methanol, filtered, and concentrated the filtrate. To the crude was added ethyl acetate and saturated $NaHCO_3$, the organics were dried with sodium sulfate and concentrated to give (+/-)-tert-butyl 3-(3-aminopyridin-4-yl)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enylcarbamate as a yellow oil in 94% yield. LCMS (*m/z*): 420.3 (MH^+), LC R_t = 3.88 min.

Synthesis of (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-2-(tert-butyldimethylsilyloxy) cyclohexylcarbamate

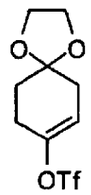


[0099] To a solution of (+/-)-tert-butyl 3-(3-aminopyridin-4-yl)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enylcarbamate (1.0 equiv.) in MeOH (0.1 M) was added Pd/C (20% by wt) and the reaction was stirred under a hydrogen balloon for 18 h. LC/MS of the reaction indicated mixture of diastereomers, the reaction was filtered, washed with EtOAc and concentrated the filtrate. The crude material was purified via prep-HPLC (in DMSO), and the pure fractions were combined, neutralized with solid $NaHCO_3$, extracted with ethyl acetate, washed with brine, dried under Na_2SO_4, and concentrated to give product A (8% yield) and product B (51% yield).

Product A: LCMS (*m/z*): 422.4 (MH^+), LC R_t = 3.75 min.

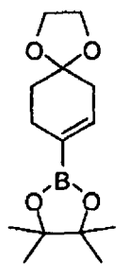
Product B: LCMS (*m/z*): 422.4 (MH^+), LC R_t =3.94 min.

Synthesis of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



[0100] 1,4-Dioxaspiro[4.5]decan-8-one (1.0 equiv) was dissolved in Ether (0.1 M) and stirred at -15 °C then 1M NaHMDS (1.05 equiv.) was added and stirred for 70 min then Tf_2O (1.05 equiv.) added and reaction allowed to slowly warm to rt. The mixture was stirred for 28 hr, washed with sat. aq. $NaHCO_3$ and then water. Aqueous layers combined and extracted with ether. Organic layers combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column (ethyl ether : hexanes = 1 : 4) to give 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (65%). LC/MS (*m/z*): MH^+=289.0, Rt=0.97. HPLC Rt=3.77.

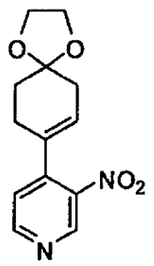
Synthesis of 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane



[0101] A solution of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethane-sulfonate (1.0 equiv.) in dioxane (0.5 M) was purged with nitrogen for 30 min. Then 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.0 equiv.), KOAc (3.0 equiv.), Pd(dppf)Cl_2-DCM (0.2 equiv.) were added and the solution was stirred in a sealed bomb at 80 °C. The reaction was filtered over a pad of celite, then to the filtrate was added ethyl acetate, and washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column (ethyl acetate : hexanes = 1 : 1) to give 4,4,5,5-tetramethyl-2-

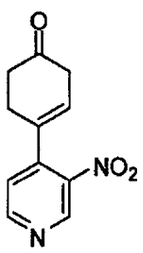
(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (95%). LC/MS (*m/z*): MH^+=267.1, Rt=0.95.

Synthesis of 3-nitro-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridine



[0102] A solution of DME (0.2 M) and 2M aq. sodium carbonate (1.7 equiv.) was purged with nitrogen for 20 min. Then 4-chloro-3-nitropyridine (1.6 equiv.), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (1.0 equiv.), $Pd(dppf)Cl_2$-DCM (0.05 equiv.) were added and stirred in a sealed bomb at 110 °C. The reaction was stirred at that temperature for 3.5 hours. The reaction was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column (ethyl acetate : hexanes = 1 : 1 with 10% methanol) to give 3-nitro-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridine (83%). LC/MS (*m/z*): MH^+=263.2, Rt=0.71.

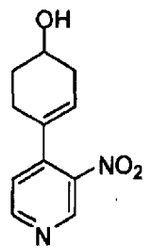
Synthesis of 4-(3-nitropyridin-4-yl)cyclohex-3-enone



[0103] A mixture of 3-nitro-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridine (1.0 equiv.) in 20% TFA in CH_2Cl_2 (0.2 M) was stirred at room temperature overnight. The solvents were removed under reduced pressure. The residue was dissolved with ethyl acetate (200 mL), and washed with sat $NaHCO_3$ (30mL), and sat NaCl (30mL). The organic was dried with $MgSO_4$, filtered and concentrated to give 4-(3-nitropyridin-4-

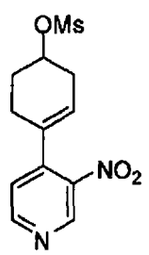
yl)cyclohex-3-enone (85%). The crude product was used to next step without further purification. LC/MS (*m/z*): MH^+=218.9, Rt=0.60

Synthesis of 4-(3-nitropyridin-4-yl)cyclohex-3-enol



[0104] To a solution of 4-(3-nitropyridin-4-yl)cyclohex-3-enone (1.0 eq) in methanol (0.2 M) was added sodium borohydride (1.8 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr. Methanol was removed under reduced pressure. The residue was dissolved with ethyl acetate (200 mL), and washed with sat. NaCl (30mL). The organic was dried with $MgSO_4$, filtered and concentrated to give 4-(3-nitropyridin-4-yl)cyclohex-3-enol (85%). The crude product was used in the next step without further purification. LC/MS (*m/z*): MH^+=221.0, Rt=0.55

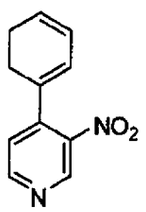
Synthesis of 4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate



[0105] To a solution of 4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) and DIPEA (2.5 equiv.) in CH_2Cl_2 (0.15 M) was added methanesulfonyl chloride (1.8 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with sat NaCl (30 mL). The organic was dried $MgSO_4$, filtered and concentrated to give 4-(3-nitropyridin-4-yl)cyclohex-3-enyl

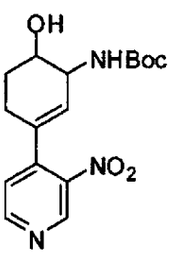
methanesulfonate (93%). The residue was used in the next step without further purification. LC/MS (*m/z*): MH^+=299.0, Rt=0.70

Synthesis of 4-(cyclohexa-1,3-dienyl)-3-nitropyridine



[0106] To a solution of 4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv) in tetrahydrofuran (0.1 M) was added DBU (1.8 equiv.) at room temperature. The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with sat NaCl (30mL). The organic was dried with $MgSO_4$, filtered and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 4-(cyclohexa-1,3-dienyl)-3-nitropyridine. LC/MS (*m/z*): MH^+=203.2, Rt=0.85.

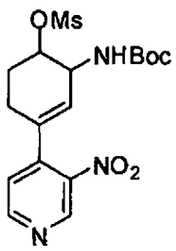
Synthesis of (+/-)-tert-butyl 6-hydroxy-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



[0107] To a solution of (+/-)-2-azido-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in Pyridine and NH_4OH (8:1, 0.23 M) was added trimethylphosphine (3.0 equiv.) at room temperature. The mixture was stirred at room temperature for 3 hours. Solvents were removed. To the residue was added ethanol. Then ethanol was removed *in vacuo* to ensure removal of the ammonia totally. The residue was dissolved in 1,4-dioxane and sat. aq. sodium bicarbonate, and then Boc_2O (1.0 eq) in THF were added to

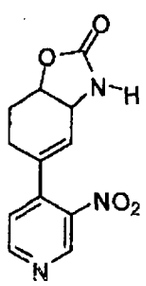
the mixture. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, and washed with sat NaCl. The organic was dried with $MgSO_4$, filtered and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give (+/-)-tert-butyl 6-hydroxy-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (82%). LC/MS (*m/z*): MH^+=336.0, Rt=0.71

Synthesis of (+/-)-2-(tert-butoxycarbonylamino)-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate



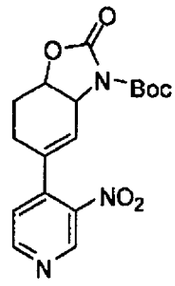
[0108] To a solution of (+/-)-tert-butyl 6-hydroxy-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) and triethyl amine (1.5 equiv.) in CH_2Cl_2 (0.2 M) was added methanesulfonyl chloride (1.2 equiv.) at 0 °C. The mixture was stirred for 2 hours at that temperature. The reaction mixture was diluted with ethyl acetate, and washed with sat NaCl. The organic was dried with $MgSO_4$, filtered and concentrated to give (+/-)-2-(tert-butoxycarbonylamino)-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (85%), which was used in the next step without further purification. LC/MS (*m/z*): MH^+=414.0, Rt=0.82

Synthesis of (+/-)-5-(3-nitropyridin-4-yl)-3,3a,7,7a-tetrahydrobenzo[d]oxazol-2(6H)-one



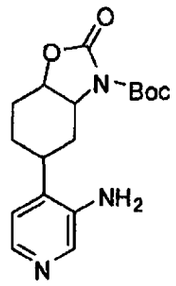
[0109] The mixture of (+/-)-2-(tert-butoxycarbonylamino)-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv.) in pyridine (0.21 M) was stirred at 110 °C for 10 min in microwave. Pyridine was removed under reduced pressure. The residue was dissolved in ethyl acetate, and washed with sat NaCl. The organic was dried with $MgSO_4$, filtered and concentrated to give (+/-)-5-(3-nitropyridin-4-yl)-3,3a,7,7a-tetrahydrobenzo[d]oxazol-2(6H)-one (85%), which was used in the next step without further purification. LC/MS (*m/z*): MH^+=262.1, Rt=0.49

Synthesis of (+/-)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate



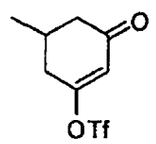
[0110] To a solution of (+/-)-5-(3-nitropyridin-4-yl)-3,3a,7,7a-tetrahydrobenzo[d]oxazol-2(6H)-one (1.0 equiv.), TEA (1.8 equiv.), and catalytic amount DMAP in CH_2Cl_2 (0.19 M) was added di-tert-butyl dicarbonate (1.2 eqiv) at room temperature. The reaction mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with sat NaCl (30mL). The organic was dried with $MgSO_4$, filtered and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give (+/-)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (98%). LC/MS (*m/z*): MH^+=306.0, Rt=0.75

Synthesis of (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-2-oxohexahydrobenzo[d]Oxazole-3(2H)-carboxylate



[0111] To a solution of (+/-)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in methanol and ethyl acetate (1:1, 0.1 M) was added 10% Pd/C (0.1 equiv.). The resulting mixture was stirred under H_2 atmosphere for 6 hours. The solid was removed by filtration. The filtrate was concentrated under reduced pressure to give (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate (87%), which was used in the next step without further purification. LC/MS (*m/z*): MH^+=334.1, Rt=0.51.

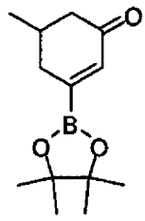
Synthesis of 5-methyl-3-oxocyclohex-1-enyltrifluoromethanesulfonate



[0112] To a solution of 5-methylcyclohexane-1,3-dione (1.0 equiv.) in DCM (0.5M) was added Na_2CO_3 (1.1 equiv.) and cooled to 0 °C. Added Tf_2O (1.0 equiv.) in DCM (5.0 M) dropwise over 1 hr at 0°C under a nitrogen atmosphere. Upon addition, the reaction was stirred for 1 hr at room temperature (dark red solution). The solution was filtered and the filtrate was quenched by careful addition of saturated $NaHCO_3$ with vigorous stirring until pH=7. The solution was transferred to a separatory funnel and the layers were separated. The organic layer was washed with brine, dried with Na_2SO_4, filtered, concentrated under vacuo and dried under high vacuum for 15 min to yield 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate as light yellow oil in 78% yield.

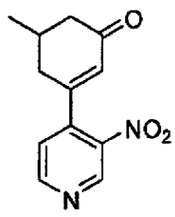
The triflate decomposes upon storage and should be used immediately for the next reaction. LC/MS=259.1/300.1 (M+H and M+CH_3CN); Rt = 0.86 min, LC = 3.84 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 6.05 (s, 1H), 2.70 (dd, J=17.2, 4.3, 1H), 2.53 (dd, J=16.6, 3.7, 1H), 2.48-2.31 (m, 2H), 2.16 (dd, J=16.4, 11.7, 1H), 1.16 (d, J=5.9, 3H).

Synthesis of 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone



[0113] To a solution of 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 equiv.) in degassed dioxane (0.7 M) was added bis(pinacolato)diboron (2.0 equiv.), KOAc (3.0 equiv.), and Pd(dppf)Cl_2-DCM (0.03 equiv.). The reaction was heated to 80 °C for 10 h (initial heating at large scale results in exothermic formation of an orange foam on top of the solution, the heating bath should be removed until the foam retracts, reheating to 80 °C at this point appears to be fine), then cooled to room temperature and filtered through a coarse frit glass funnel. The cake was rinsed with more dioxane and the filtrate solution was used for the next step without further purification. LC/MS = 155.1 (M+H of boronic acid); Rt = 0.41 min, LC = 1.37 min.

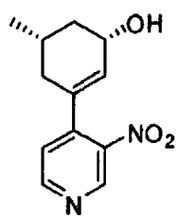
Synthesis of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone



[0114] To a solution of 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (1.0 equiv.) in degassed dioxane (0.5 M) and 2M Na_2CO_3 (2 equiv.) was added 4-chloro-3-nitropyridine (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.). The reaction was placed under a reflux condenser and heated in an oil bath to 110°C for 1 h. Cooled to room temperature, filtered through a pad of Celite, washed the pad with

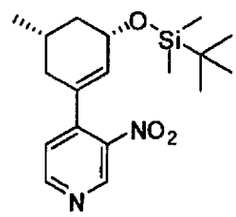
ethyl acetate and concentrated the filtrate under vacuo. The residue was further pumped at 80 °C on a rotary evaporator for one hour to remove boronate by-products (M+H = 101) via sublimation. The residue was partitioned between brine and ethyl acetate, and the layers were separated, the aqueous phase was further extracted with ethyl acetate (4x), the organics were combined, dried over sodium sulfate, filtered, and concentrated. The crude was purified via silica gel chromatography loading in DCM and eluting with 2-50% ethyl acetate and hexanes. The pure fractions were concentrated in vacuo to yield an orange oil. The oil was placed under high vacuum (~500 mtorr) with seed crystals overnight to yield an orange solid. The solid was further purified via trituration in hexanes to yield 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (48% 2 steps). LC/MS = 233.2 (M+H); Rt = 0.69 min, LC = 2.70 min. ^{1}H-NMR (400 MHz, $CdCl_3$) δ ppm: 9.31 (s, 1H), 8.88 (d, J=5.1, 1H), 7.30 (d, J=5.1, 1H), 6.00 (d, J=2.4, 1H), 2.62 (dd, J=16.4, 3.5, 1H), 2.53-2.34 (m, 3H), 2.23 (dd, J=16.1, 11.7, 1H), 1.16 (d, J=6.3, 3H).

Synthesis of cis-(+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



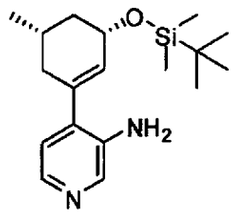
[0115] To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 equiv.) in EtOH (0.3 M) was added $CeCl_3$-$7H_2O$ (1.2 equiv.). The reaction was cooled to 0°C, then $NaBH_4$ (1.2 equiv.) was added in portions. Stirred for 1 h at 0°C, then quenched by adding water, concentrated to remove the EtOH, added EtOAc, extracted the organics, washed with brine, then dried with Na_2SO_4, filtered and concentrated to yield cis-(+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (94%). LC/MS = 235.2 (M+H), LC = 2.62 min.

Synthesis of 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine



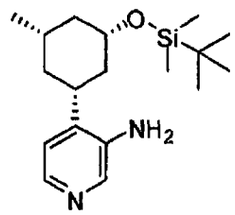
[0116] To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in DMF (0.5 M) was added imidazole (4.0 equiv.) and TBDMSCl (2.5 equiv.). After stirring for 18 hours the solution was portioned between EtOAc and H_2O and separated. After washing further with H_2O (3x) and $NaCl_{(sat.)}$, drying over $MgSO_4$, filtering and removal of solvents, 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine was obtained (85%). LC/MS = 349.2 (M+H), LC = 5.99 min.

Synthesis of 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)pyridin-3-amine



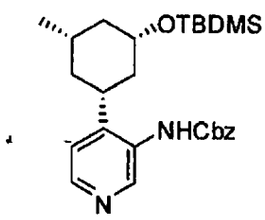
[0117] A heterogeneous solution of 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (1.0 eq.) and iron (6.0 eq) in acetic acid, at a concentration of 0.4 M, was stirred vigorously for 2 hours. The mixture was then passed through a celite pad, eluting with MeOH. Upon removal of the volatiles *in vacuo*, the residue was dissolved in EtOAc, washed with $Na_2CO_{3\ (sat.)}$, $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and the volatiles were removed *in vacuo* yielding 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)pyridin-3-amine (78%). LCMS (*m/z*): 319.3 (MH^+); LC R_t = 3.77 min.

Synthesis of 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine



[0118] To a solution of 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 15 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine (90%). LCMS (*m/z*): 321.3 (MH^+); LC R_t = 3.85 min.

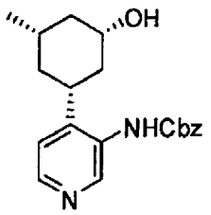
Synthesis of cis (+/-) benzyl 4-3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl) pyridin-3-ylcarbamate



[0119] To a solution of cis-(+/-)-4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine in dichloromethane at a concentration of 0.5 M was added benzyl 2,5-dioxopyrrolidin-1-yl carbonate (1.1 equiv.) and DMAP (0.05 equiv.). After stirring for 16 hours at rt, additional benzyl 2,5-dioxopyrrolidin-1-yl carbonate (0.55 equiv.) and DMAP (0.03 equiv.) were added. After stirring for an additional 24 hours at rt, additional benzyl 2,5-dioxopyrrolidin-1-yl carbonate (0.1 equiv.) and DMAP (0.03 equiv.) were added. After stirring for 18 more hours the solution was partitioned between EtOAc and $Na_2CO_{3(sat.)}$ and separated. Upon further washing with $Na_2CO_{3(sat.)}$ (2x) and $NaCl_{(sat.)}$, drying over $MgSO_4$, filtering and removal of solvents, cis (+/-) benzyl

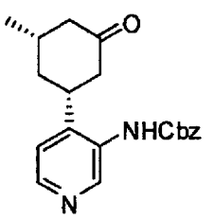
4-3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-ylcarbamate was obtained. The crude material was used as is. LC/MS = 455.3 (M+H), LC = 4.39 min.

Synthesis of cis-(+/-)benzyl 4-(3-hydroxy-5-methylcyclohexyl)pyridin-3-ylcarbamate



[0120] A solution of cis (+/-) benzyl 4-3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-ylcarbamate in 1:2:1 6N HCl/THF/MeOH at a concentration of 0.1 M was stirred at rt for 6 hours. The pH was than adjusted to pH=7 by addition of 6N NaOH and the volatiles were removed *in vacuo*. The aqueous layer was extracted with EtOAc and the organic was washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and upon removal of the volatiles in vacuo, cis-(+/-)benzyl 4-(3-hydroxy-5-methylcyclohexyl)pyridin-3-ylcarbamate was obtained. The crude material was used as is. LC/MS = 341.2 (M+H), LC = 2.38 min.

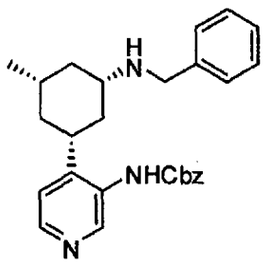
Synthesis of cis (+/-)-benzyl 4-(3-methyl-5-oxocyclohexyl)pyridin-3-ylcarbamate



[0121] To a 0 °C solution of cis-(+/-)-benzyl 4-(3-hydroxy-5-methyl-cyclohexyl)pyridin-3-ylcarbamate in wet CH_2Cl_2 at a concentration of 0.16 M was added Dess-Martin Periodinane (1.5 equiv.) and the solution was stirred for 18 hours as it warmed to rt. The solution was partitioned between EtOAc and 1:1 10% $Na_2S_2O_3/NaHCO_{3(sat.)}$ and separated. Upon further washing with 1:1 10% $Na_2S_2O_3/NaHCO_{3(sat.)}$ (2x) and $NaCl_{(sat.)}$, drying over $MgSO_4$, filtering, removal of solvents and purification by silica gel chromatography (75-100% EtOAc/hexanes), cis-

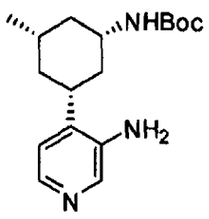
(+/-)-benzyl-4-(3-methyl-5-oxocyclohexyl)pyridin-3-ylcarbamate was obtained as a white solid (53%, 5 steps). LC/MS = 339.2 (M+H).

Synthesis of cis-(+/-)- benzyl 4-(-3-(benzylamino)-5-methylcyclohexyl)pyridin-3-ylcarbamate



[0122] A solution of cis-(+/-)-benzyl-4-(3-methyl-5-oxocyclohexyl)pyridin-3-ylcarbamate (1.0 equiv) and benzylamine (3.0 equiv) in MeOH, at a concentration of 0.25 M, was stirred at rt for 2 hours. Upon cooling in a -78 °C bath, $LiBH_4$ (1.1 equiv, 2.0 M in THF) was added and the solution was allowed to warm to rt with stirring over 16 hours. The solution was partitioned between EtOAc and $NaHCO_{3(sat.)}$, separated, washed further with $NaHCO_{3(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and after removal of volatiles *in vacuo*, cis-(+/-)- benzyl 4-(-3-(benzylamino)-5-methylcyclohexyl)pyridin-3-ylcarbamate was obtained as a 4:1 mixture of isomers, with the all cis as predominant LC/MS = 430.3 (M+H), LC = 0.62 min.

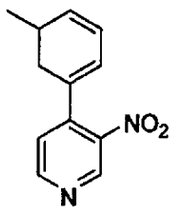
Synthesis of cis (+/-)-tert-butyl (-3-(3-aminopyridin-4-yl)-5-methylcyclohexylcarbamate



[0123] To a solution of cis-(+/-)- benzyl 4-(-3-(benzylamino)-5-methylcyclohexyl)pyridin-3-ylcarbamate was (1.0 equiv.) in methanol, at a concentration of 0.07 M, was added 20% palladium hydroxide on carbon (0.2 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the reaction was purged with Ar, Boc_2O (1.0 equiv.) was added and

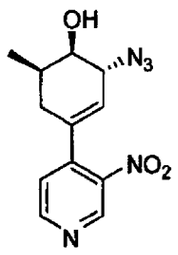
the solution was stirred for 8 hours. Additional Boc_2O (1.0 equiv.) was added and the solution was stirred for 16 more hours. At this time the mixture was filtered through a pad of celite eluting with methanol. Upon removal of volatiles in vacuo, purification by silica gel chromatography (2.5-2.5 $MeOH/CH_2Cl_2$ with 0.1% DIEA) and recrystallization from 10% EtOAc/hexanes yielded cis (+/-)-tert-butyl (-3-(3-aminopyridin-4-yl)-5-methylcyclohexylcarbamate (49%). LCMS (*m/z*): 306.3 (MH^+), LC R_t = 2.59 min . Pure enantiomers could be obtained by chiral chromatography.

Synthesis of (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine



[0124] To a solution of (+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in dioxane (0.1M) was added p-TSA (1.0 equiv.), and the reaction was stirred at 100 °C for 3 h. The solution was cooled to room temperature, then passed through a pad of neutral alumina eluting with EtOAc to yield (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine as a yellow oil in 68% yield. LC/MS = 217.1 (M+H), LC = 3.908 min.

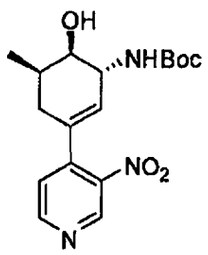
Synthesis of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol



[0125] To a solution of (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine (1.0 equiv.) in DCM (0.1 M) at 0 °C was added m-CPBA (1.1 equiv.) and the reaction was allowed to warm to room temperature. After 3 hours, the mixture was quenched with

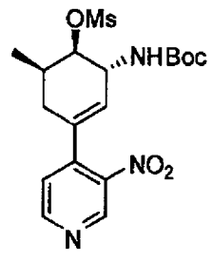
saturated $NaHCO_3$, extracted with DCM, and the organic phase was dried with sodium sulfate, filtered, and concentrated to give a yellow oil. The crude was dissolved in ethanol and water (3:1, 0.1 M), and sodium azide (2.0 equiv.) and ammonium chloride (2.0 equiv.) were added. The reaction was stirred for 4 hours, then concentrated *in vacuo*. To the crude was added ethyl acetate and water, the organic phase was washed with brine, dried with sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol as an oil in 49% yield. LC/MS = 276.1 (M+H), Rt = 0.71 min.

Synthesis of tert-butyl (+/-)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



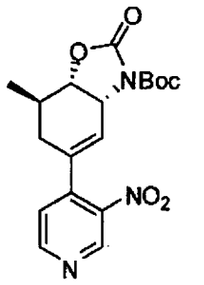
[0126] To a solution of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in pyridine and ammonium hydroxide (8:1, 0.08 M) was added trimethylphosphine (3.0 equiv.) and the brown solution was stirred at room temperature for 2 hours. Ethanol was added to the mixture and the solution was concentrated under vacuo (2x). The crude mixture was then dissolved in dioxane and sat. $NaHCO_3$ (1:1, 0.08 M) and Boc_2O (1.0 equiv.) was added. The solution was stirred at room temperature for 2 hours, then partitioned between ethyl acetate and water. The organic phase was dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford tert-butyl (+/-)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate in 69% yield. LC/MS = 350.1 (M+H), Rt = 0.76 min.

Synthesis of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl) cyclohex-3-enyl methanesulfonate



[0127] To a solution of tert-butyl (+/-)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in DCM (0.09 M) was added triethyl amine (1.5 equiv.). The reaction mixture was cooled to 0 °C and MsCl (1.2 equiv.) was added to the reaction and stirred for 3 hours. To the solution was added water, the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate as a white foam in 65% yield. LC/MS = 428.2 (M+H), Rt = 0.88 min.

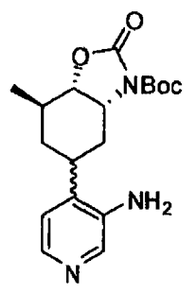
Synthesis of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate



[0128] A solution of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv.) in pyridine (0.2 M) in a microwave vessel was heated to 110 °C for 10 min. The orange solution was then concentrated to dryness and worked up by partitioning between ethyl acetate and water. The organic phase was dried with sodium sulfate, filtered and concentrated. The crude material was dissolved in DCM (0.2 M) and triethyl amine (1.8 equiv.) was added to the reaction, followed by Boc_2O (1.2 eqiv.). After stirring at room temperature for 40 min,

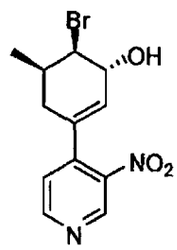
the reaction was concentrated in vacuo and purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate as a white foam in 66% yield. LC/MS = 376.0 (M+H), Rt = 0.87 min.

Synthesis of (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate



[0129] To a solution of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in MeOH and ethyl acetate (1:1, 0.07 M) was added 10% Pd/C (0.1 equiv.) and the reaction was stirred at room temperature under an atmosphere of hydrogen. Upon completion of the reaction, the solution was filtered through a pad of Celite, washed with MeOH and ethyl acetate, the filtrate was concentrated to dryness under vacuo to give (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate as a mixture of diastereomers in >99% yield. LC/MS = 348.2 (M+H), Rt = 0.50 min.

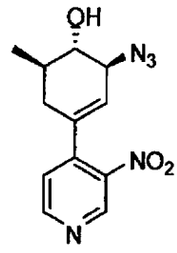
Synthesis of (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



[0130] To a solution of 4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine (1.0 equiv.) in THF and water (1:1, 0.13 M) was added NBS (1.5 equiv.) and the reaction was stirred at room temperature for 30 min. Upon completion, ethyl acetate and water were

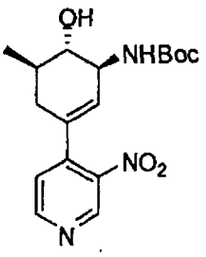
added to the reaction, the organic phase was dried with brine, then sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol as a yellow oil in 80% yield. LC/MS = 315.0/313.0 (M+H), LC = 2.966 min.

Synthesis of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol



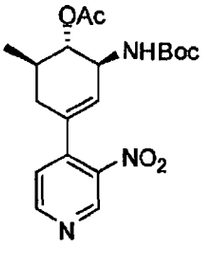
[0131] To a solution of (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in THF (0.1 M) was added potassium tert-butoxide (1.5 equiv.). The reaction turned from orange to black almost immediately. By TLC, the formation of product is clean in 30 min. Quenched by adding saturated ammonium chloride and ethyl acetate. The organic phase was dried with brine, then sodium sulfate, filtered, and concentrated. The crude product was dissolved in ethanol and water (3:1, 0.1 M), and ammonium chloride (2.0 equiv) and sodium azide (2.0 equiv.) were added. The dark orange reaction was stirred at room temperature overnight. The conversion to product is clean as indicated by LC/MS. The reaction was concentrated to remove the ethanol, ethyl acetate and water were added, and the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol in 55% yield. LC/MS = 276.0 (M+H), LC = 2.803 min.

Synthesis of (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



[0132] To a solution of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in pyridine and ammonium hydroxide (8:1, 0.08 M) was added trimethylphosphine (3.0 equiv.) and the brown solution was stirred at room temperature for 2 h. Upon completion, EtOH was added and the solution was concentrated in vacuo. More ethanol was added and the reaction was concentrated again. Dioxane and sat. $NaHCO_3$ (1:1, 0.08 M) were added to the crude, followed by Boc_2O (1.0 equiv.). Stirred the reaction mixture at room temperature for 2h, then added water and ethyl acetate. The organic phase was dried with $MgSO_4$, and concentrated. The crude product was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (59%). LC/MS = 350.1 (M+H), Rt: 0.76 min.

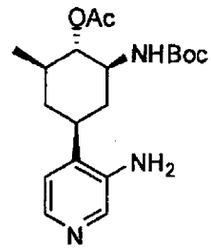
Synthesis of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl acetate



[0133] To a solution of (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in pyridine (0.1 M) was added Ac_2O (2.0 equiv.) and the reaction was stirred at room temperature overnight. Upon completion, the reaction was concentrated to dryness, then worked-up with ethyl acetate and water. The

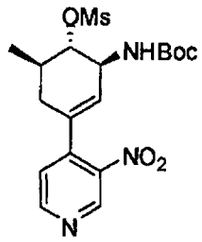
organic phase was dried with brine, then sodium sulfate, filtered, and concentrated to give (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl acetate in 94% yield. LC/MS = 392.2 (M+H), Rt = 0.94 min.

Synthesis of (+/-)-4-(3-aminopyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate



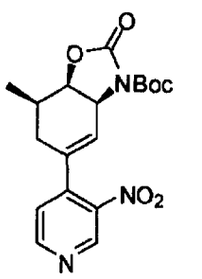
[0134] To a degassed solution of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl acetate (1.0 equiv.) in MeOH and EtOAc (1:1, 0.1 M) was added 10% Pd/C (0.1 equiv.) and the reaction was stirred at room temperature under a hydrogen balloon for 3 days. Upon completion, the solution was filtered through a pad of Celite, the pad was washed with ethyl acetate and the filtrate was concentrated. The crude material contained about 10% of the undesired isomer. The crude was dissolved in ethyl acetate (~20%) and hexanes and heated until all dissolved. The solution was allowed to sit at room temperature for 2 days. The precipitate was then collected to give (+/-)-4-(3-aminopyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate as the pure product in 59% yield. LC/MS = 364.3 (M+H), Rt = 0.63 min.

Synthesis of 2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate



[0135] To a solution of tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in DCM (0.09 M) was added triethylamine (1.5 equiv.) and the reaction was cooled to 0 °C. MsCl (1.2 equiv.) was added to the reaction and stirred for 3 h. Another 1.0 equiv. of MsCl was added to the reaction and stirred for another 2 h. Worked up the reaction by adding water, the organic phase was dried with brine, sodium sulfate, and concentrated. The crude product was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford 2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate as a white foam in 65% yield. LC/MS = 428.2 (M+H), LC: 3.542 min.

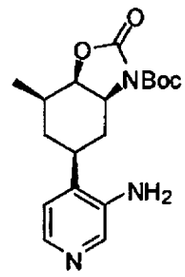
Synthesis of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate



[0136] A solution of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv.) in pyridine (0.2 M) was heated in the microwave at 110 °C for 10 min. The orange reaction was then concentrated under vacuo, the crude was dissolved in ethyl acetate and water, the organic phase was dried with sodium sulfate and concentrated under vacuo. The crude material

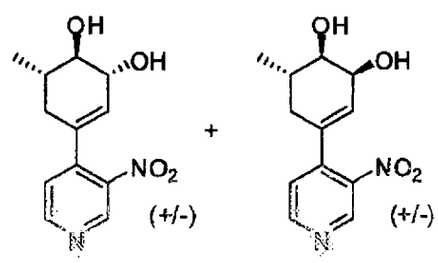
was dissolved in DCM (0.2 M), triethylamine (1.8 equiv.) was added, followed by Boc_2O (1.2 equiv.). The reaction was stirred for 40 min, then concentrated to dryness. The crude material was purified via silica gel column chromatography eluting with hexane and ethyl acetate (1:1) to afford (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate as a white foam in 66% yield. LC/MS = 376.0 (M+H), LC: 3.424 min.

Synthesis of (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate



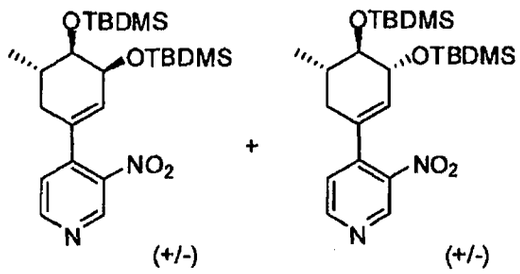
[0137] To a degassed solution of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in MeOH and EtOAc (1:1, 0.1 M) was added 10% Pd/C (0.1 equiv.). The reaction was stirred under a hydrogen balloon overnight. Upon completion, the solution was filtered through a pad of Celite and the pad was washed with ethyl acetate. The filtrate was concentrated under vacuo to give (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate as the desired product as a yellow foam in 93% yield. LC/MS = 348.1 (M+H), Rt = 055 min.

Synthesis of ((+/-)-(1R,2R,6S)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-ene-1,2-diol and (+/-)-(1R,2S,6S)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-ene-1,2-diol)



[0138] To a solution of (+/-)-(1S,5S,6S)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in THF (0.1M) was added potassium tert-butoxide (1.5 equiv.) at room temperature. The reaction mixture was stirred for 10 min. The reaction mixture was quenched with NH_4Cl solution and worked up with EtOAc by washing with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered off, and dried in vacuo. The crude product was used for next step without further purification. R_f = 0.5 (50% EtOAc/Hexanes). LCMS: MH+ 251.2 (as a diol), R_t =0.49 min. To a solution of crude (+/-)-4-((1S,5S)-5-methyl-7-oxabicyclo[4.1.0]hept-2-en-3-yl)-3-nitropyridine (1.0 equiv.) in 2:1 CH_3CN/H_2O (0.1 M) was added acetic acid (0.3 equiv.) at room temperature. The reaction mixture was stirred for 16 h at room temperature. After quenched with $NaHCO_3$ solution, the reaction mixture was concentrated to remove the majority of CH_3CN and the residue was partitioned between EtOAc and water. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. A mixture of diols ((+/-)-(1R,2R,6S)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-ene-1,2-diol and (+/-)-(1R,2S,6S)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-ene-1,2-diol) was obtained in 33.1% yield as a white solid by flash column chromatography. R_f = 0.3 (100% EtOAc; diols were not separable on TLC). LCMS: MH+ 251.2, R_t =0.49 min.

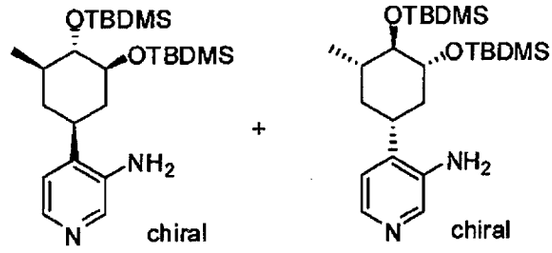
Synthesis of (+/-)-4-((3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine and (+/-)-4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine



[0139] To a solution of a mixture of diols (1.0 equiv) in DMF (0.3 M) was added TBDMSCl (7.0 equiv.) and imidazole (9 equiv.) at room temperature. The reaction mixture was stirred at room temperature overnight. After quenched with sat $NaHCO_3$, The reaction mixture was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and

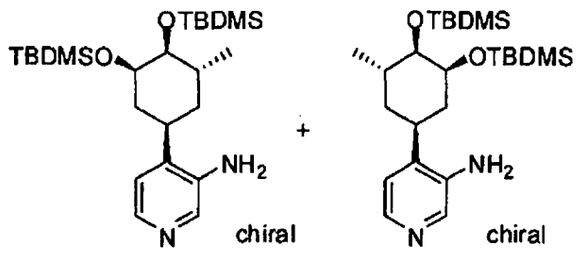
concentrated in vacuo. The mixture was purified by sequential automated silica column chromatography (gradient eluting with EtOAc and Hexanes) and preparative reverse phase HPLC (55%-95% acetonitrile in water, then run 5%-95% acetonitrile in water to yield (+/-)-4-((3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (27.2%) and (+/-)-4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (50.2%). LCMS: MH+ 479.2, R_t =1.60 and 1.63 min.

Synthesis of 4-((1S,3S,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine and of 4-((1R,3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine



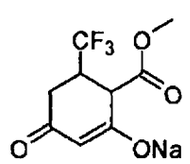
[0140] To a solution of (+/-)-4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) in ethanol/EtOAc, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with EtOAc. The volatiles were removed *in vacuo* and the crude material was purified by automated silica column chromatography (R_f = 0.2, 40% EtOAc in Heptane) to yield pure racemic product. LCMS: MH+ 451.3, Rt =1.35 min. The racemic compound was resolved by chiral chromatography (IC column, 1 mL/min, 5%IPA in Heptane) to yield 4-((1S,3S,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine (6.01 min) and 4-((1R,3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine (8.34 min).

Synthesis of 4-((1R,3R,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine and of 4-((1S,3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine



[0141] To a solution of (+/-)-4-((3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) in ethanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with ethanol. The volatiles were removed *in vacuo* and the crude material was purified by automated silica column chromatography (R_f = 0.2, 40% EtOAc in Heptane) to yield pure racemic product (50.4%). LCMS: MH+ 451.3, R_t =1.35 min. The racemic compound was resolved by chiral chromatography (IC column, 1 mL/min, 5%IPA in Heptane) to yield 4-((1R,3R,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine (6.98 min) and 4-((1S,3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine (8.67 min).

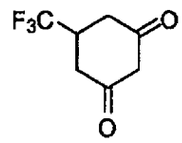
Synthesis of sodium 6-(methoxycarbonyl)-3-oxo-5-(trifluoromethyl)cyclohex-1-enolate



[0142] To a freshly prepared solution of sodium (1.0 eq) in t-BuOH (1 M) was added ethyl acetoacetate (1.0 eq) by dropwise and the mixture stirred on an ice bath for an additional 15 min. ethyl 4,4,4-trifluorocrotonate (1.0 eq) was added dropwise and the mixture stirred at room temperature for an additional 30 min. After refluxing for 2 h, the mixture was cooled and hexanes was added. The precipitate was filtered without further

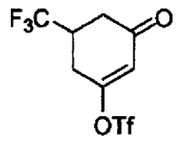
purification to give sodium 6-(methoxycarbonyl)-3-oxo-5-(trifluoromethyl)cyclohex-1-enolate (46%). LC/MS (*m/z*): MH^+ = 253.1, Rt = 0.70min.

Synthesis of 5-(trifluoromethyl)cyclohexane-1,3-dione



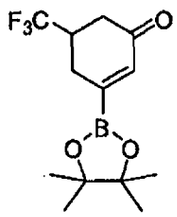
[0143] Sodium 6-(Methoxycarbonyl)-3-oxo-5-(trifluoromethyl)cyclohex-1-enolate (1.0 eq) was dissolved in 1M NaOH (1.0 eq), and the mixture refluxed for 1 h. After cooling to room temperature, the mixture was acidified with 5 M sulfuric acid. The mixture was extracted with EtOAc. After washing with water, the organic layer was dried over magnesium sulfate, the solvent was removed under reduced pressure to give 5-(trifluoromethyl)cyclohexane-1,3-dione, which was used to the next step without further purification (98%). LC/MS (*m/z*): MH^+ =181.1, Rt = 0.55min.

Synthesis of 3-oxo-5-(trifluoromethyl)cyclohex-1-enyl trifluoromethanesulfonate



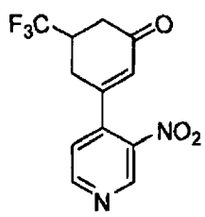
[0144] To a suspension of 5-(trifluoromethyl)cyclohexane-1,3-dione (1.0 eq) in DCM (0.23 M) was added TEA (1.2 eq) to give a clear solution. The mixture was cooled to 0 °C. And then Tf_2O (1.05 eq) in DCM was added dropwise. The reaction mixture was stirred at that temperature for 2 hours. The reaction mixture was diluted with DCM, and washed with water, *aq.* $NaHCO_3$, brine, and was dried over $MgSO_4$, filtered and concentrated to give 3-oxo-5-(trifluoromethyl)cyclohex-1-enyl trifluoromethanesulfonate, which was used to next step directly. LC/MS (*m/z*): MH^+ = 313.0, Rt = 1.02 min.

Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)cyclohex-2-enone



[0145] All of reagents 3-oxo-5-(trifluoromethyl)cyclohex-1-enyl trifluoromethanesulfonate (1.0 eq), NaOAc (3.0 eq), and bis(pinacolato)diboron (2.0 eq) were added to 1,4-dioxane (0.23 M) in a round bottom flask and degassed by bubbling N_2 through the mixture for 10 min. $PdCl_2(dppf).CH_2Cl_2$ adduct (0.1 eq) was added and the reaction heated to 80 °C fitted with a reflux condenser on an oil bath under N_2 for two hours. The mixture was cooled to room temperature, filtered through a coarse frit glass funnel, the cake rinsed with ~10mL 1,4-dioxane to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)cyclohex-2-enone in 1,4-dioxane, which was used to next step directly. LC/MS (*m/z*): $MH^+ = 209.1$ (boronic acid), Rt=0.60 min.

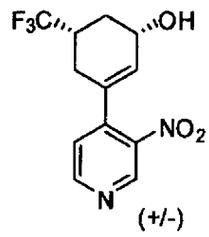
Synthesis of 3-(3-nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enone



[0146] The boronate ester 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)cyclohex-2-enone (1.0 eq) was dissolved in 1,4-dioxane (0.14 M) in a round bottom flask was degassed by bubbling N_2 through the solution for 30 minutes. 4-chloro-3-nitropyridine (1.3 eq) and *aq.* Na_2CO_3 (2M, 2.0 eq) were added and N_2 was bubbled through for 10 minutes and then $PdCl_2(dppf).CH_2Cl_2$ adduct (0.1 eq) was added. The reaction mixture was stirred at 100 °C for 2 Hours. The mixture was added EtOAc and brine. The resulting mixture was filtered through celite, the cake was washed with EtOAc. The organic layer was separated, and washed with brine, dried over MgSO4, and filtered and concentrated. The crude product was purified by silica gel chromatography

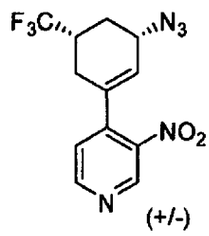
(eluted with EtOAc:Hexanes = 1:10 to 2:1) to give 3-(3-nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enone (73% for three steps from diketone). LC/MS (*m/z*): MH^+ = 287.1, Rt = 0.85 min.

Synthesis of cis-3-(3-nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enol



[0147] 3-(3-Nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enone (1.0 eq) was mixed with cerium(III) chloride heptahydrate (1.0 eq) and absolute ethanol (0.17) was added. The mixture was stirred at ambient temperature until all solids dissolved. the mixture was cooled on an ice bath and $NaBH_4$ (1.2 eq) was added portion wise. The reaction was stirred on the ice bath for 1h. The mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column (1:1 ethyl acetate and hexanes) to give cis-3-(3-nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enol (66%). LC/MS (*m/z*): MH^+ = 289.2, Rt = 0.72 min.

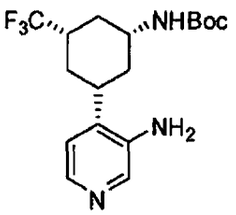
Synthesis of cis-4-(3-azido-5-(trifluoromethyl)cyclohex-1-enyl)-3-nitropyridine



[0148] To a solution of cis-3-(3-nitropyridin-4-yl)-5-(trifluoromethyl)cyclohex-2-enol (1.0 eq) in DCM (0.14 M) was added TEA (2.5 eq), and followed by MsCl (1.8 eq) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed. The residue was dissolved in DMF (0.19 M), and then the mixture was added sodium azide (1.2 eq). The resulting mixture was stirred at room temperature for 1 hour. Another 1.2 eq of sodium azide was added.

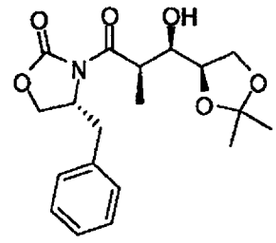
The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and heptane, and washed with sat NaCl. The organic was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column (1:1 ethyl acetate and hexanes) to give cis-4-(3-azido-5-(trifluoromethyl)cyclohex-1-enyl)-3-nitropyridine (58%). LC/MS (*m/z*): MH^+ = 314.1, Rt=0.96 min.

Synthesis of tert-butyl (1R,3R,5S)-3-(3-aminopyridin-4-yl)-5-(trifluoromethyl)cyclohexylcarbamate



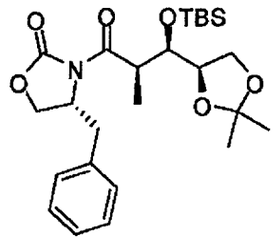
[0149] A solution of cis-4-(3-azido-5-(trifluoromethyl)cyclohex-1-enyl)-3-nitropyridine (1.0 eq) in Ethanol (0.13 M) was bubbled with N_2 for 20 min. Then the reaction mixture was added Boc-anhydride (1.5 eq) and Pd/C (0.2 eq). The reaction mixture was stirred at room temperature under H_2 atmosphere overnight. Solid was removed by filtration over celite and rinsed with EtOH. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give racemic cis-3-(3-aminopyridin-4-yl)-5-(trifluoromethyl)cyclohexylcarbamate (57%). LC/MS (m/z): MH+ = 360.2 , Rt = 0.72 min. The enantiomerically pure tert-butyl (1R,3R,5S)-3-(3-aminopyridin-4-yl)-5-(trifluoromethyl)cyclohexylcarbamate and N-(4-((1S,3S,5R)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide were resolved by chiral HPLC (For analysis R_t = 8.14 min and 10.59 min respectively; heptane:isopropanol= 90:10 (v:v), Chiralcel IC 100 x 4.6 mm at 1 mL/min. For preparative separation, heptane:isopropanol = 90:10 (v:v), Chiralcel IC 250 x 20 mm at 15 mL/min).

Synthesis of (R)-4-benzyl-3-((2R,3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-methylpropanoyl)oxazolidin-2-one



[0150] (R)-4-benzyl-3-((2R,3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-methylpropanoyl)oxazolidin-2-one was prepared in the reported manner (Proc.Nat.Acad.Sciences, 101, 33, 2004, pages 12042-12047) for the enantiomeric compound by starting with (R)-4-benzyl-3-propionyloxazolidin-2-one and R-glyceraldehyde acetonide.

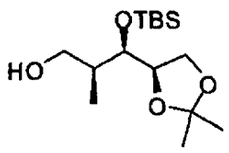
Synthesis of (R)-4-benzyl-3-((2R,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanoyl)oxazolidin-2-one



[0151] (R)-4-benzyl-3-((2R,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanoyl)oxazolidin-2-one was prepared in the reported manner (Proc.Nat.Acad.Sciences, 101, 33, 2004, pages 12042-12047) for the enantiomeric compound by starting with (R)-4-benzyl-3-((2R,3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-methylpropanoyl)oxazolidin-2-one.

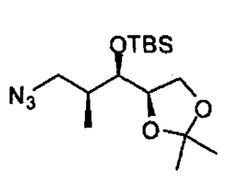
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Synthesis of (2S,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol



[0152] To a solution of (R)-4-benzyl-3-((2R,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanoyl)oxazolidin-2-one (1.0 equiv.) and ethanol (3.0 equiv.) in THF (0.09 M) was added $LiBH_4$ (1.0 equiv.) at -40°C. The reaction mixture was allowed to warm up to rt slowly and stirred at that temperature for 12 hours. The solution was cooled back to -40°C and additional $LiBH_4$ (0.3 equiv.) was added. After warming back up to rt and stirring for 2 hours the solution was then diluted with diethyl ether and 1N NaOH) was added. The resulting mixture was extracted with ethyl acetate, the organic layer was separated, washed with $NaCl_{(sat.)}$, dried over magnesium sulfate, filtered, and concentrated. The residue was purified via silica gel column chromatography (10-30% EtOAc/n-heptanes) yielding (2S,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol in (75%). LC/MS = 247.1 (M+H-ketal-H_2O), R_t = 0.64 min.

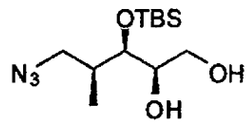
Synthesis of ((1R,2S)-3-azido-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)(tert-butyl)dimethylsilane



[0153] To a solution of (2S,3R)-3-(tert-butyldimethylsilyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol (1.0 equiv.), DIAD (2.0 equiv.), and PPh_3 (2.0 equiv.) in THF (0.18 M) was added DPPA (1.0 equiv., 1M solution in THF). The reaction mixture was stirred at room temperature overnight. Upon removal of the volatiles under vacuo, the residue was purified by silica gel column chromatography (2-3-5% EtOAc/n-heptanes) yielding ((1R,2S)-3-azido-1-((R)-2,2-dimethyl-1,3-dioxolan-4-

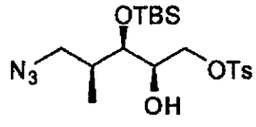
yl)-2-methylpropoxy)(tert-butyl)dimethylsilane (62%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.04-4.10 (m, 1H), 3.94 (dd, J=8.0, 6.4, 1H), 3.72 (d, J=7.2, 1H), 3.53 (t, J=8.0, 1H), 3.36 (dd, J=12, 8.0, 1H), 3.19 (dd, J=12.0, 6.7, 1H), 1.52-1.60 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 0.92 (d, J=7.2, 3H), 0.90 (s, 9 H), 0.12 (s, 3H), 0.09 (s, 3H).

Synthesis of (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-4-methylpentane-1,2-diol



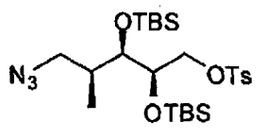
[0154] To a solution of ((1R,2S)-3-azido-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)(tert-butyl)dimethylsilane (1.0 equiv.) in MeOH (0.1 M) was added PPTS (1.0 equiv.) and the mixture was stirred at rt for 14 hours, 50°C for 2 hours and 80°C for 1 hour. The volatiles were removed under vacuo and the residue was purified via silica gel column chromatography (10-25% EtOAc/n-heptanes) yielding (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-4-methylpentane-1,2-diol (40%).

Synthesis of (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-2-hydroxy-4-methylpentyl 4-methylbenzenesulfonate



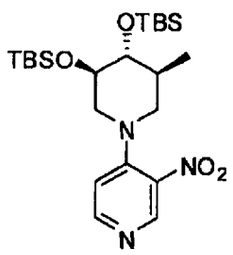
[0155] To a solution of tert-butyl (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-1-hydroxy-4-methylpentan-2-ylcarbamate (1.0 equiv.) in pyridine (0.2 M) was added pTsCl (1.3 equiv.) at 0 °C. The mixture held at this temperature for 16 hours. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (10-15-20% EtOAc/n-heptanes) yielding (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-2-hydroxy-4-methylpentyl 4-methylbenzenesulfonate.

Synthesis of (2R,3R,4S)-5-azido-2,3-bis(tert-butyldimethylsilyloxy)-4-methylpentyl 4-methylbenzenesulfonate



[0156] To a solution of (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-2-hydroxy-4-methylpentyl 4-methylbenzenesulfonate (1.0 equiv.) and 2,6-lutidine (3.4 equiv.) was added TBDMSOTf (1.7 equiv.) at 0°C. The solution was stirred for 7 hours as it warmed to rt. The solution was diluted with EtOAc, washed with 10% $CuSO_4$, H_2O, $Na_2CO_{3(sat.)}$, $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (2.5-5-10-20% EtOAc/n-heptanes) yielding (2R,3R,4S)-5-azido-2,3-bis(tert-butyldimethylsilyloxy)-4-methylpentyl 4-methylbenzenesulfonate (75%).

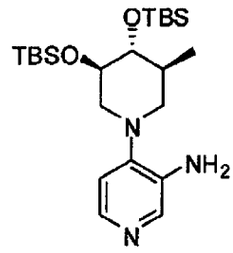
Synthesis of 4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylpiperidin-1-yl)-3-nitropyridine



[0157] A solution of (2R,3R,4S)-5-azido-2,3-bis(tert-butyldimethylsilyloxy)-4-methylpentyl 4-methylbenzenesulfonate in EtOH (0.05 M) was degassed with argon. DIEA (1.5 equiv.) was added, followed by 10% Pd/C (0.1 equiv.). The reaction mixture was stirred under a hydrogen balloon for 3 hours. The solution was degassed and purged to argon, at which time 4-chloro-3-nitropyridine (1.5 equiv.) and additional DIEA (1.5 equiv.) were added. After stirring at rt for 15 hours the solution was filtered to remove the Pd/C and the volatiles were removed in vacuo. The residue was diluted with ethyl acetate and washed with $Na_2CO_{3(sat.)}$, $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (10-15%

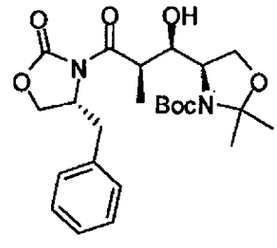
EtOAc/n-heptanes) yielding 4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylpiperidin-1-yl)-3-nitropyridine (40%). LC/MS = 482.4 (M+H), R_t = 1.26 min.

Synthesis of 4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylpiperidin-1-yl)pyridin-3-amine



[0158] To a solution of 4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylpiperidin-1-yl)-3-nitropyridine (1.0 equiv.) in ethanol, at a concentration of 0.05 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with ethanol. The volatiles were removed in vacuo yielding 4-((3R,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylpiperidin-1-yl)pyridin-3-amine. LC/MS = 452.4 (M+H), R_t = 1.31 min.

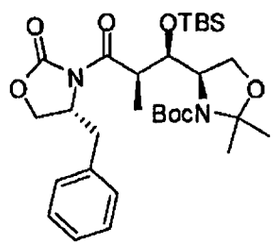
Synthesis of (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-hydroxy-2-methyl-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate



[0159] To a solution of (R)-4-benzyl-3-propionyloxazolidin-2-one (1.0 equiv.) in DCM (0.13 M) was added $TiCl_4$ (1.0 equiv.) at -40 °C. The mixture was stirred at -40 °C for 10 min (yellow suspension), then DIPEA (2.5 equiv.) was added (dark red solution) and stirred at 0 °C for 20 min. (R)-tert-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (1.0 equiv.) in DCM (0.5 M) was then added dropwise and the resulting mixture was stirred for 1.5 hours. The reaction was quenched by the addition of aqueous

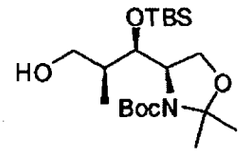
ammonium chloride and the mixture was extracted with ethyl acetate. The organic phase was separated, washed with brine, dried with magnesium sulfate, filtered, and concentrated. The residue was purified via column chromatography eluting with ethyl acetate and hexanes (1:4) to give (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-hydroxy-2-methyl-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate as the major product (5:2) in 58% yield. LC/MS = 363.3 (M+H-Boc), Rt = 1.09 min.

Synthesis of (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-(tert-butyldimethylsilyloxy)-2-methyl-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate



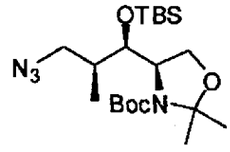
[0160] To a solution of (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-hydroxy-2-methyl-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (1.0 equiv.) and lutidine (1.8 equiv.) in DCM (0.1M) was added TBSOTf (1.4 equiv.) at -40 °C. The reaction mixture was stirred at -40 °C for 2 hours. The solution was diluted with ethyl acetate and washed with sat. $NaHCO_3$, sat. NaCl, dried with magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate and hexanes (1:4) to give (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-(tert-butyldimethylsilyloxy)-2-methyl-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate as the major product (5:2) in 83% yield. LC/MS = 577.3 (M+H), Rt = 1.33 min (Frac 65%-95% method).

Synthesis of (R)-tert-butyl 4-((1R,2S)-1-(tert-butyldimethylsilyloxy)-3-hydroxy-2-methylpropyl)-2,2-dimethyloxazolidine-3-carboxylate



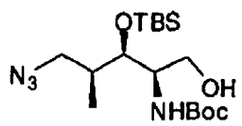
[0161] To a solution of (R)-tert-butyl 4-((1R,2R)-3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-1-(tert-butyldimethylsilyloxy)-2-methyl-3-oxopropyl)-2,2-dimethyl-oxazolidine-3-carboxylate (1.0 equiv.) and ethanol (3.0 equiv.) in THF (0.09 M) was added $LiBH_4$ (3.0 equiv.) at -30 °C. The reaction mixture was allowed to warm up to 0 °C and stirred at that temperature for 3 hours. The solution was then diluted with diethyl ether and 1N NaOH was added. The resulting mixture was extracted with ethyl acetate, the organic layer was separated, washed with sat. NaCl, dried over magnesium sulfate, filtered, and concentrated. The residue was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:4) to give (R)-tert-butyl 4-((1R,2S)-1-(tert-butyldimethylsilyloxy)-3-hydroxy-2-methylpropyl)-2,2-dimethyloxazol-idine-3-carboxylate as the major product (5:2 ratio) in 71% yield. LC/MS = 304.3 (M+H-Boc), Rt = 0.95 min (Frac 65%-95% method).

Synthesis of (R)-tert-butyl 4-((1R,2S)-3-azido-1-(tert-butyldimethylsilyloxy)-2-methylpropyl)-2,2-dimethyloxazolidine-3-carboxylate



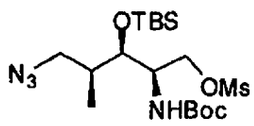
[0162] To a solution of (R)-tert-butyl 4-((1R,2S)-1-(tert-butyldimethyl-silyloxy)-3-hydroxy-2-methylpropyl)-2,2-dimethyloxazolidine-3-carboxylate (1.0 equiv.), DIAD (2.0 equiv.), and PPh_3 (2.0 equiv.) in THF (0.18 M) was added DPPA (2.0 equiv., 1M solution in THF). The reaction mixture was stirred at room temperature overnight. Upon removal of the volatiles under vacuo, the residue was purified by silica gel column chromatography eluting with ethyl acetate and hexanes (1:6) to give (R)-tert-butyl 4-((1R,2S)-3-azido-1-(tert-butyldimethylsilyloxy)-2-methylpropyl)-2,2-dimethyloxazol-idine-3-carboxylate as the major product (5:2) in 86% yield. LC/MS = 329.3 (M+H-Boc), Rt = 1.40 min (Frac 65%-95% method).

Synthesis of tert-butyl (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-1-hydroxy-4-methylpentan-2-ylcarbamate



[0163] To a solution of (R)-tert-butyl 4-((1R,2S)-3-azido-1-(tert-butyldimethylsilyloxy)-2-methylpropyl)-2,2-dimethyloxazolidine-3-carboxylate (1.0 equiv.) in EtOH (0.1 M) was added PPTS (1.3 equiv.) and the mixture was refluxed for 2 days. The volatiles were removed under vacuo, the residue was dissolved in DCM (0.1 M) and DIEA (1.5 equiv.) and Boc_2O (1.0 equiv.) were added to the reaction mixture. The solution was stirred for 3 hours at room temperature. The solvents were removed under reduced pressure and the residue was diluted with ethyl acetate, washed with water, aqueous $NaHSO_4$, aqueous $NaHCO_3$, sat. NaCl, the organic phase was dried with magnesium sulfate, filtered, and concentrated. The residue was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:3) to give tert-butyl (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-1-hydroxy-4-methylpentan-2-ylcarbamate as the major isomer (5:2) in 70% yield. LC/MS = 289.3 (M+H-Boc), Rt = 0.76 min (Frac 65%-95% method).

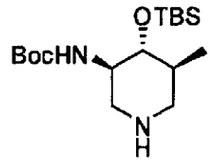
Synthesis of (2R,3R,4S)-5-azido-2-(tert-butoxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-4-methylpentyl methanesulfonate



[0164] To a solution of tert-butyl (2R,3R,4S)-5-azido-3-(tert-butyldimethylsilyloxy)-1-hydroxy-4-methylpentan-2-ylcarbamate (1.0 equiv.) in pyridine (0.2 M) was added MsCl (1.3 equiv.) followed by DMAP (catalytic amount) at 0 °C. The mixture was stirred at that temperature for 1 hour. The solution was diluted with ether and ethyl acetate (4:1), washed with aq. $NaHSO_4$, sat. $NaHCO_3$, brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate and hexanes (1:3) to give (2R,3R,4S)-5-azido-2-(tert-butoxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-4-methylpentyl

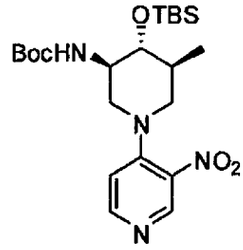
methanesulfonate as the major isomer (5:2) in 90% yield. LC/MS = 367.3 (M+H-Boc), Rt = 0.81 min (Frac 65%-95% method).

Synthesis of tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methylpiperidin-3-ylcarbamate



[0165] A solution of (2R,3R,4S)-5-azido-2-(tert-butoxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-4-methylpentyl methanesulfonate in MeOH (0.09 M) was degassed with nitrogen for 20 min. DIEA (2.5 equiv.) was added, followed by 10% Pd/C (0.1 equiv.). The reaction mixture was stirred under a hydrogen balloon for 2 hours. The solution was filtered and the filtrate was concentrated under vacuo to afford tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methylpiperidin-3-ylcarbamate as the major isomer (5:2) in >99% yield. LC/MS = 345.2 (M+H-Boc), Rt = 0.95 and 0.99 min.

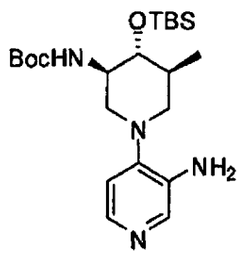
Synthesis of tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



[0166] To a solution of tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methylpiperidin-3-ylcarbamate (1.0 equiv.) in i-PrOH (0.09 M) was added DIEA (2.5 equiv.) and 4-chloro-3-nitropyridine (1.5 equiv.). The reaction mixture was stirred at 60 °C for 2 hours. The volatiles were removed under vacuo, the residue was diluted with ethyl acetate and washed with sat. NaCl. The organic phase was dried with magnesium sulfate, filtered, and concentrated. The crude material was purified by silica gel column

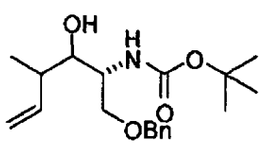
chromatography eluting with ethyl acetate and hexanes (1:2) to give tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate in 76% yield. LC/MS = 467.3 (M+H), Rt = 1.09 min.

Synthesis of tert-butyl (3R,4R,5S)-1-(3-aminopyridin-4-yl)-4-(tert-butyldimethylsilyloxy)-5-methylpiperidin-3-ylcarbamate



[0167] A solution of tert-butyl (3R,4R,5S)-4-(tert-butyldimethylsilyloxy)-5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (1.0 equiv.) in MeOH (0.05 M) was degassed with nitrogen for 20 min. 10% Pd/C (0.2 equiv.) was added to the mixture and the solution was stirred under a hydrogen balloon for 3 hours. The reaction was filtered and the filtrate was concentrated under reduced pressure to give tert-butyl (3R,4R,5S)-1-(3-aminopyridin-4-yl)-4-(tert-butyldimethylsilyloxy)-5-methylpiperidin-3-ylcarbamate as the desired product in 94% yield. LC/MS = 437.4 (M+H), Rt = 1.08 min. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.95 (d, J = 6.0 Hz, 1H), 6.76 (d, J = 6.0 Hz, 1H), 4.44 (br s, 1H), 3.74 (br s, 2H), 3.59-3.55 (m, 1H), 3.25-3.13 (m, 2H), 2.47-2.35 (m, 2H), 1.89 (br s, 2H), 1.44 (s, 9H), 1.04 (d, J = 6.0 , 3H), 0.92 (s, 9H), 0.13 (d, J = 9.0, 6H).

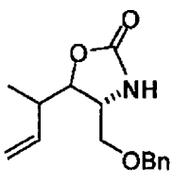
Synthesis of tert-butyl (2R)-1-(benzyloxy)-3-hydroxy-4-methylhex-5-en-2-ylcarbamate



[0168] To a solution of N-Boc, O-benzyl-D-Serine aldehyde (1.0 equiv) in DCM (0.1 M) at -78°C under an Ar atmosphere was added (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 equiv) and the clear solution stirred for 16 hours as

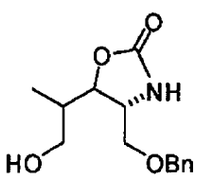
it warmed to rt. The solution was added to EtOAc and was washed with H_2O (3x), and $NaCl_{(sat.)}$, dried over $MgSO_4$ and purified by silica gel chromatography (15% EtOAc/hexanes) to yield tert-butyl (2R)-1-(benzyloxy)-3-hydroxy-4-methylhex-5-en-2-ylcarbamate (54%) as a 3:1 mixture of isomers as judged by ^1H NMR. LCMS (*m/z*): 236.3 (MH^+-Boc); LC R_t = 4.37 and 4.51 min.

Synthesis of (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one



[0169] To a solution of (2R)-1-(benzyloxy)-3-hydroxy-4-methylhex-5-en-2- in THF (0.1 M) was added 60% sodium hydride in mineral oil (1.5 equiv.). After stirring for 3 days, the reaction was quenched by addition of $NH_4Cl_{(sat.)}$ and solution was diluted with EtOAc and washed with $NH_4Cl_{(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$ and purified by silica gel chromatography (50% EtOAc/hexanes) to yield (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one (89%) as a 3:1 mixture. LCMS (*m/z*): 262.2 (MH^+); LC R_t = 3.47 min.

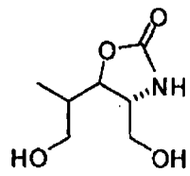
Synthesis of (4R)-4-(benzyloxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one



[0170] To a solution of (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one (1.0 equiv.) in 2:1 MeOH/ H_2O (0.04 M) was added osmium tetroxide 4% in H_2O (0.07 equiv) and sodium periodate (3.0 equiv.). After stirring for 3 hours, the white precipitate was filtered and rinsed with EtOAc. The combined filtrate was concentrated in vacuo and the residue was dissolved in EtOAc, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and concentrated. The crude aldehyde was

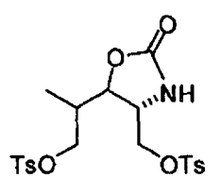
dissolved in EtOH (0.08 M) and upon cooling to 0°C, sodium borohydride (2.0 equiv.) was added. After stirring for 15 hours and coming to room temperature the reaction was quenched by addition of H_2O. After stirring for 20 minutes, the EtOH was removed in vacuo, EtOAc was added and the solution was washed with 1N HCl, $NaHCO_{3(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and concentrated yielding after purification by silica gel chromatography (4R)-4-(benzyloxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one as a 3:1 mixture of isomers (60%). LCMS (*m/z*): 266.1 (MH^+); LC R_t = 2.28 min.

Synthesis of (4R)-4-(hydroxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one



[0171] To a solution of (4R)-4-(benzyloxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 15 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding (4R)-4-(hydroxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one (99%). LCMS (*m/z*): 176.1 (MH^+).

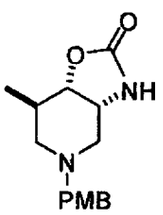
Synthesis of 2-((4R)-2-oxo-4-(tosyloxymethyl)oxazolidin-5-yl)-propyl 4-methylbenzenesulfonate

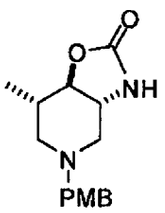


[0172] To a solution of (4R)-4-(hydroxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one (1.0 equiv.) in pyridine (0.15 M) at 0°C was added p-toluenesulfonylchloride (2.1 equiv.). The solution was allowed to warm to rt as it stirred for 14 hours, at which time EtOAc was added and the solution was washed with H_2O(3x), $CuSO_{4(sat.)}$ (2x), H_2O , $Na_2CO_{3(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated

and purified by silica gel chromatography (75%EtOAc/hexanes eluent) yielding 2-((4R)-2-oxo-4-(tosyloxymethyl)oxazolidin-5-yl)propyl 4-methylbenzenesulfonate (68%). LCMS (*m/z*): 484.1 (MH^+); LC R_t = 4.06 min.

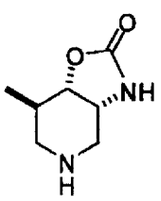
Synthesis of (3aR,7R,7aS)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one and (3aR,7S,7aR)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one





[0173] A solution of 2-((4R)-2-oxo-4-(tosyloxymethyl)oxazolidin-5-yl)propyl 4-methylbenzenesulfonate (1.0 equiv.), diisopropylethyl amine (3.0 equiv.) and para-methoxybenzylamine (1.5 equiv.) in NMP (0.05 M) was heated at 100°C for 14 hours. The solution was purified directly by RP HPLC. The product fractions were desalted by addition to EtOAc and $Na_2CO_{3(s)}$, washed further with NaCl(sat.), dried over $MgSO_4$ and concentrated yielding two separate isomers of (3aR,7R,7aS)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one and (3aR,7S,7aR)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (27% and 8%). LCMS (*m/z*): 277.2 (MH^+) at 0.40 and 0.42 min.

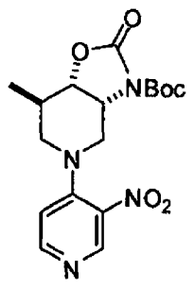
Synthesis of (3aR,7R,7aS)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one



[0174] To a solution of (3aR,7R,7aS)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 20% palladium hydroxide on carbon (0.3 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 2 hours. At this time the mixture was filtered through a pad of celite eluting with methanol.

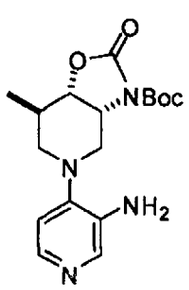
The volatiles were removed *in vacuo* yielding (3aR,7R,7aS)-7-methylhexahydro-oxazolo[4,5-c]pyridin-2(3H)-one (99%). LCMS (*m/z*): 157.1 (MH^+) at 0.16 min.

Synthesis of (3aR,7R,7aS)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0175] A solution of 4-chloro-3-nitropyridine (1.3 equiv.) and (3aR,7R,7aS)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (1.5 equiv.) in CH_2Cl_2, at a concentration of 0.1 M, was stirred at rt for 48 hours at which piperidine (0.4 equiv) was added to consume excess 4-chloro-3-nitropyridine. After stirring for an additional 2 hours, di-tert-butyl dicarbonate (2.0 equiv.) and dimethylaminopyridine (0.1 equiv.) were added. After stirring for 4 hours, the solution was partitioned between EtOAc and $NaHCO_{3\,(sat.)}$, was washed further with $NaHCO_{3\,(sat.)}$, and $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and purified by silica gel chromatography yielding (3aR,7R,7aS)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)carboxylate (62%). LCMS (*m/z*): 379.0 (MH^+) at 0.58 min..

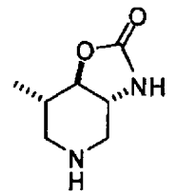
Synthesis of (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0176] To a solution of (3aR,7R,7aS)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate (1.0 equiv.) in methanol, at

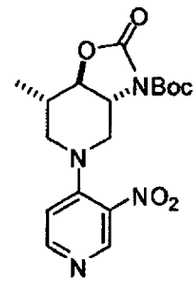
a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.06 min.

Synthesis of (3aR,7S,7aR)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one



[0177] To a solution of (3aR,7S,7aR)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 20% palladium hydroxide on carbon (0.3 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 2 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding (3aR,7S,7aR)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (99%). LCMS (*m/z*): 157.1 (MH^+) at 0.17 min.

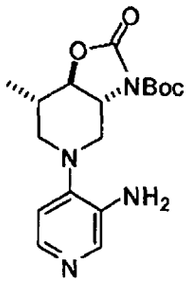
Synthesis of (3aR,7S,7aR)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0178] A solution of 4-chloro-3-nitropyridine (1.3 equiv.) and (3aR,7S,7aR)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (1.5 equiv.) in CH_2Cl_2, at a concentration of 0.1 M, was stirred at rt for 48 hours at which piperidine (0.4 equiv) was

added to consume excess 4-chloro-3-nitropyridine. After stirring for an additional 2 hours, di-tert-butyl dicarbonate (2.0 equiv.) and dimethylaminopyridine (0.1 equiv.) were added. After stirring for 4 hours, the solution was partitioned between EtOAc and $NaHCO_{3\,(sat.)}$, was washed further with $NaHCO_{3\,(sat.)}$, and $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and purified by silica gel chromatography (75% EtOAc/hexanes eluent) yielding (3aR,7S,7aR)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate (35%). LCMS (*m/z*): 379.0 (MH^+). LC R_t = 2.42 min.

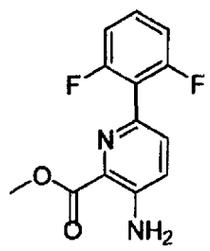
Synthesis of (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0179] To a solution of (3aR,7S,7aR)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding (3aR,7S,7aR)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.18 min.

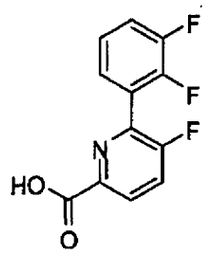
Method 1

Synthesis of methyl 3-amino-6-(2,6-difluorophenyl)picolinate



[0180] A solution of methyl 3-amino-6-bromopicolinate (1.0 equiv.), 2,6-difluorophenyl-boronic acid (3.0 equiv), and $Pd(dppf)Cl_2$-DCM (0.1 equiv.) in 3:1 DME/ 2M Na_2CO_3 (0.5 M) was subjected to microwave irradiation at 120 °C for 15 min intervals. The reaction was filtered and washed with EtOAc. The organic was partitioned with H_2O (25mL), was further washed with $NaCl_{(sat.)}$ (25mL), was dried over $MgSO_4$, and the volatiles were removed *in vacuo*. The residue was diluted in EtOAc and passed through a silica gel plug and the volatiles were removed *in vacuo* yielding methyl 3-amino-6-(2,6-difluorophenyl)picolinate (47%). LCMS (*m/z*): 265.1 (MH^+); LC R_t = 2.70 min

Synthesis of 6-(2,3-difluorophenyl)-5-fluoropicolinic acid

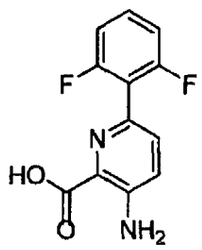


[0181] To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 2,3-difluorophenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with

1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 6-(2,3-difluorophenyl)-5-fluoropicolinic acid in 78%. LC/MS = 254.1 (M+H), Rt = 0.75 min.

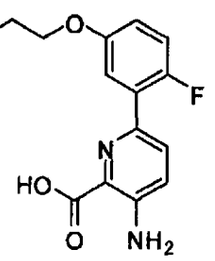
Method 2

Synthesis of 3-amino-6-(2,6-difluorophenyl)picolinic acid



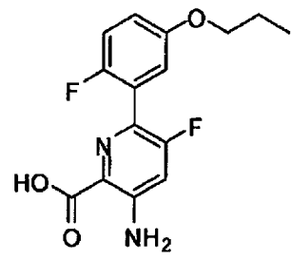
[0182] To a solution of methyl 3-amino-6-(2,6-difluorophenyl)picolinate (1.0 equiv) in THF (0.5 M), was added 1M LiOH (4.0 equiv). After stirring for 4 hours at 60 °C, 1 N HCl (4.0 equiv.) was added and the THF was removed *in vacuo*. The resulting solid was filtered and rinsed with cold H_2O (3 x 20mL) to yield 3-amino-6-(2,6-difluorophenyl)picolinic acid (90%). LCMS (*m/z*): 251.1 (MH^+); LC R_t = 2.1 min.

Synthesis of 3-amino-6-(2-fluoro-5-propoxyphenyl)picolinic acid



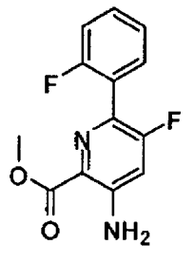
[0183] Method 1 was followed using 3-amino-6-bromopicolinic acid (1.0 equiv.) and 2-fluoro-5-propoxyphenylboronic acid (1.5 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) to give 3-amino-6-(2-fluoro-5-propoxyphenyl)picolinic acid in 75% yield. LC/MS = 291.0 (M+H), Rt = 0.81 min.

Synthesis of 3-amino-5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinic acid



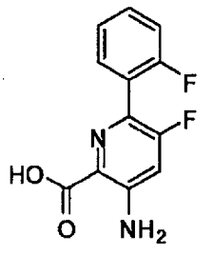
[0184] Method 1 was followed using 3-amino-6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2-fluoro-5-propoxyphenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 3-amino-5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinic acid in 28% yield. LC/MS = 309.1 (M+H), Rt = 1.00 min.

Synthesis of methyl 3-amino-5-fluoro-6-(2-fluorophenyl)picolinate



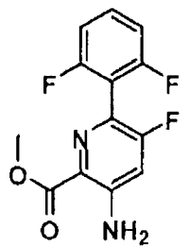
[0185] Method 1 was followed using methyl 3-amino-6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-fluoro-phenylboronic acid (1.5 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give methyl 3-amino-5-fluoro-6-(2-fluorophenyl)picolinate in >99% yield. LC/MS = 265.0 (M+H), Rt = 0.77 min.

Synthesis of 3-amino-5-fluoro-6-(2-fluorophenyl)picolinic acid



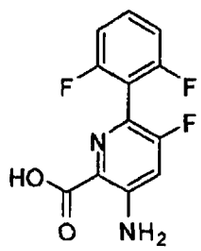
[0186] Method 2 was followed using 3-amino-5-fluoro-6-(2-fluorophenyl)picolinate (1.0 equiv.) and LiOH (5.0 equiv.) to give 3-amino-5-fluoro-6-(2-fluorophenyl)picolinic acid in 90% yield. LC/MS = 251.1 (M+H), Rt = 0.80 min.

Synthesis of methyl 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate



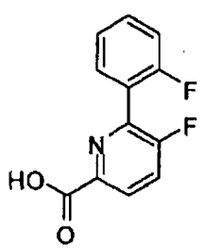
[0187] Method 1 was followed using methyl 3-amino-6-bromo-5-fluoropicolinate (1.0 equiv.) and 2,6-difluorophenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate in 94% yield. LC/MS = 283.0 (M+H), Rt = 0.76 min.

Synthesis of 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinic acid



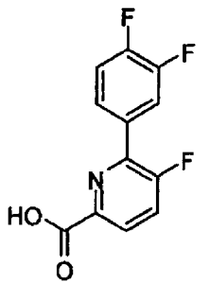
[0188] Method 2 was followed using 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate (1.0 equiv.) and LiOH (1.0 equiv.) to give 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinic acid in 79% yield. LC/MS = 269.0 (M+H), Rt = 0.79 min.

Synthesis of 5-fluoro-6-(2-fluorophenyl)picolinic acid



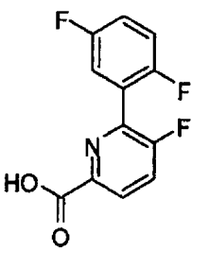
[0189] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2-fluorophenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 5-fluoro-6-(2-fluorophenyl)picolinic acid in 43% yield. LC/MS = 236.1 (M+H), Rt = 0.72 min.

Synthesis of 6-(3,4-difluorophenyl)-5-fluoropicolinic acid



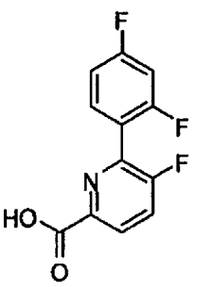
[0190] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 3,4-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) to give 6-(3,4-difluorophenyl)-5-fluoropicolinic acid in 70% yield. LC/MS = 254.1 (M+H), Rt = 0.81 min.

Synthesis of 6-(2,5-difluorophenyl)-5-fluoropicolinic acid



[0191] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2,5-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) to give 6-(2,5-difluorophenyl)-5-fluoropicolinic acid in 80% yield. LC/MS = 254.1 (M+H), Rt = 0.74 min.

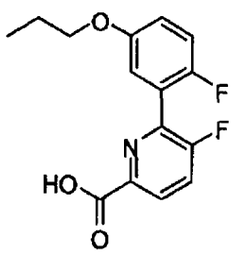
Synthesis of 6-(2,4-difluorophenyl)-5-fluoropicolinic acid



[0192] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2,4-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05

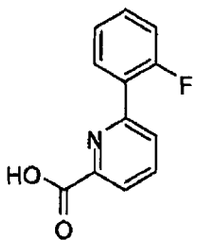
equiv.) to give 6-(2,4-difluorophenyl)-5-fluoropicolinic acid in 79% yield. LC/MS = 254.1 (M+H), Rt = 0.75 min.

Synthesis of 5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinic acid



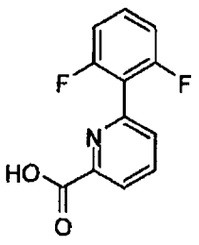
[0193] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2-fluoro-5-propoxyphenylboronic acid (1.5 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinic acid. LC/MS = 294.2 (M+H), Rt = 0.95 min.

Synthesis of 6-(2-fluorophenyl)picolinic acid



[0194] Method 1 was followed using 6-bromopicolinic acid (1.0 equiv.) and 2-fluorophenylboronic acid (1.5 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 6-(2-fluorophenyl)picolinic acid in 93% yield. LC/MS = 218.0 (M+H), Rt = 0.66 min.

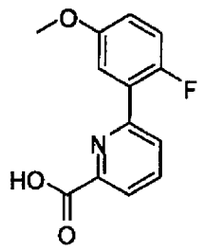
Synthesis of 6-(2,6-difluorophenyl)picolinic acid



[0195] Method 1 was followed using 6-bromopicolinic acid (1.0 equiv.) and 2,6-difluorophenylboronic acid (1.5 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give

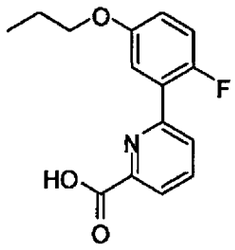
6-(2,6-difluorophenyl)picolinic acid in 38% yield. LC/MS = 236.0 (M+H), Rt = 0.87 min.

Synthesis of 6-(2-fluoro-5-methoxyphenyl)picolinic acid



[0196] Method 1 was followed using 6-bromopicolinic acid (1.0 equiv.) and 2-fluoro-5-methoxyphenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.15 equiv.) to give 6-(2-fluoro-5-methoxyphenyl)picolinic acid in 95% yield. LC/MS = 248.2 (M+H), Rt = 0.78 min.

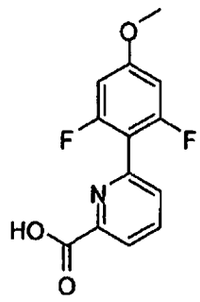
Synthesis of 6-(2-fluoro-5-propoxyphenyl)picolinic acid



[0197] Method 1 was followed using 6-bromopicolinic acid (1.0 equiv.) and 2-fluoro-5-propoxyphenylboronic acid (1.5 equiv.) and Pd(dppf)Cl_2-DCM (0.15 equiv.) to give 6-(2-fluoro-5-propoxyphenyl)picolinic acid in 20% yield. LC/MS = 276.0 (M+H), Rt = 0.87 min.

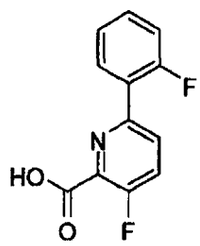
61

Synthesis of 6-(2,6-difluoro-4-methoxyphenyl)picolinic acid



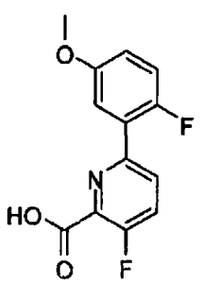
[0198] Method 1 was followed using 6-bromopicolinic acid (1.0 equiv.) and 2,6-difluoro-4-methoxyphenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.15 equiv.) to give 6-(2,6-difluoro-4-methoxyphenyl)picolinic acid in 42% yield. LC/MS = 266.1 (M+H), Rt = 0.75 min.

Synthesis of 3-fluoro-6-(2-fluorophenyl)picolinic acid



[0199] Method 1 was followed using 6-bromo-3-fluoropicolinic acid (1.0 equiv.) and 2-fluorophenylboronic acid (1.5 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 3-fluoro-6-(2-fluorophenyl)picolinic acid in 81% yield. LC/MS = 236.1 (M+H), Rt = 0.72 min.

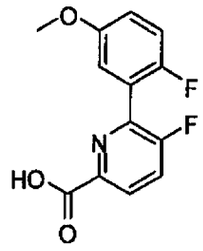
Synthesis of 3-fluoro-6-(2-fluoro-5-methoxyphenyl)picolinic acid



[0200] Method 1 was followed using 6-bromo-3-fluoropicolinic acid (1.0 equiv.) and 2-fluoro-5-methoxyphenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM

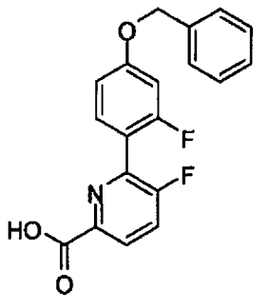
(0.15 equiv.) to give 3-fluoro-6-(2-fluoro-5-methoxyphenyl)picolinic acid in 89% yield. LC/MS = 266.1 (M+H), Rt = 0.79 min.

Synthesis of 5-fluoro-6-(2-fluoro-5-methoxyphenyl)picolinic acid



[0201] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 2-fluoro-5-methoxyphenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.15 equiv.) to give 5-fluoro-6-(2-fluoro-5-methoxyphenyl)picolinic acid in 86% yield. LC/MS = 266.1 (M+H), Rt = 0.79 min.

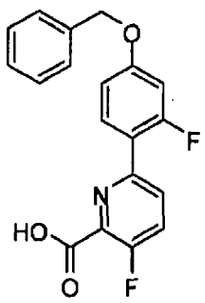
Synthesis of 6-(4-(benzyloxy)-2-fluorophenyl)-5-fluoropicolinic acid



[0202] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 4-(benzyloxy)-2-fluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.15 equiv.) to give 6-(4-(benzyloxy)-2-fluorophenyl)-5-fluoropicolinic acid in 28% yield. LC/MS = 342.1 (M+H), Rt = 1.05 min.

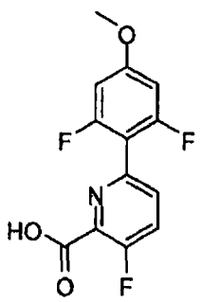
62

Synthesis of 6-(4-(benzyloxy)-2-fluorophenyl)-3-fluoropicolinic acid



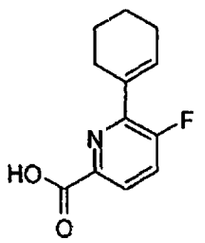
[0203] Method 1 was followed using 6-bromo-3-fluoropicolinic acid (1.0 equiv.) and 4-(benzyloxy)-2-fluorophenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.15 equiv.) to give 6-(4-(benzyloxy)-2-fluorophenyl)-3-fluoropicolinic acid in 41% yield. LC/MS = 342.1 (M+H), Rt = 1.06 min.

Synthesis of 6-(2,6-difluoro-4-methoxyphenyl)-3-fluoropicolinic acid



[0204] Method 1 was followed using 6-bromo-3-fluoropicolinic acid (1.0 equiv.) and 2,6-difluoro-4-methoxyphenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.15 equiv.) to give 6-(2,6-difluoro-4-methoxyphenyl)-3-fluoropicolinic acid in 9% yield. LC/MS = 284.0 (M+H), Rt = 0.74 min.

Synthesis of 6-cyclohexenyl-5-fluoropicolinic acid

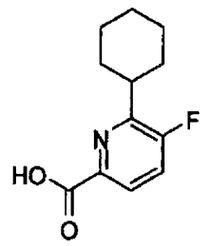


[0205] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and cyclohexenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.15 equiv.) to

give 6-cyclohexenyl-5-fluoropicolinic acid in 61 % yield. LC/MS = 222.0 (M+H), Rt = 0.52 min.

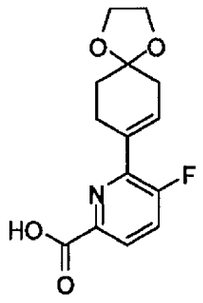
Method 3

Synthesis of 6-cyclohexyl-5-fluoropicolinic acid



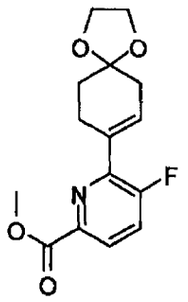
[0206] To a degassed solution of 6-cyclohexenyl-5-fluoropicolinic acid (1.0 equiv.) in MeOH (0.07M) was added 10% Pd/C (0.1 equiv.) and the reaction was stirred under a hydrogen balloon overnight. The solution was then filtered, rinsed with MeOH, and the filtrate was concentrated to afford 6-cyclohexyl-5-fluoropicolinic acid in 65% yield. LC/MS = 224.2 (M+H), Rt = 0.95 min.

Synthesis of 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinic acid



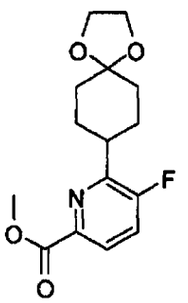
[0207] Method 1 was followed using 6-bromo-5-fluoropicolinic acid (1.0 equiv.) and 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (2.0 equiv.) and $Pd(dppf)Cl_2$-DCM (0.2 equiv.) to give 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinic acid. LC/MS = 280.2 (M+H), Rt = 0.66 min.

Synthesis of methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinate



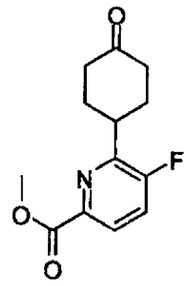
[0208] To a solution of 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinic acid (1.0 equiv.) in DCM (0.3 M) was added EDC-HCl (1.0 equiv.), DMAP (1.0 equiv.), and MeOH (10 equiv.). The reaction mixture was allowed to stir at room temperature for 5 days, then diluted with ethyl acetate, washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography eluting with 25-50% ethyl acetate in hexanes to yield methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinate as the desired product in 35% yield. LC/MS = 294.2 (M+H), Rt = 0.79 min.

Synthesis of methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]decan-8-yl)picolinate



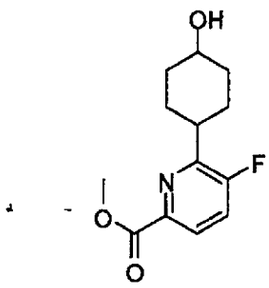
[0209] To a degassed solution of methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)picolinate (1.0 equiv.) in MeOH (0.07M) was added 10% Pd/C (0.1 equiv.) and the reaction was stirred under a hydrogen balloon overnight. The solution was then filtered, rinsed with MeOH, and the filtrate was concentrated to afford methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]decan-8-yl)picolinate in 91% yield. LC/MS = 296.2 (M+H), Rt = 0.83 min.

Synthesis of methyl 5-fluoro-6-(4-oxocyclohexyl)picolinate



[0210] To a solution of methyl 5-fluoro-6-(1,4-dioxaspiro[4.5]decan-8-yl)picolinat (1.0 equiv.) in acetone and water (1:1, 0.04 M) was added oxalic acid dehydrate (2.0 equiv.) and the reaction mixture was stirred for 3 days. The solution was then neutralized by the addition of solid $NaHCO_3$, the mixture was added to ethyl acetate and brine, the organic phase was dried over magnesium sulfate, filtered, and concentrated. Methyl 5-fluoro-6-(4-oxocyclohexyl)picolinate was obtained in 98% yield. LC/MS = 252.1 (M+H), Rt = 0.68 min.

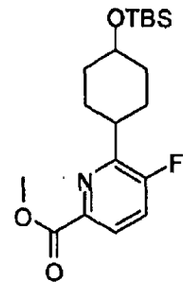
Synthesis of methyl 5-fluoro-6-(4-hydroxycyclohexyl)picolinate



[0211] To a 0 °C solution of methyl 5-fluoro-6-(4-oxocyclohexyl)picolinate (1.0 equiv.) win MeOH (0.08 M) was added $NaBH_4$. The solution was allowed to warm to room temperature overnight then partitioned between ethyl acetate and brine, the organic phase was dried over magnesium sulfate, filtered, and concentrated to give methyl 5-fluoro-6-(4-hydroxycyclohexyl)picolinate as a mixture of two isomers (5:1). LC/MS = 254.2 (M+H), Rt = 0.63 min.

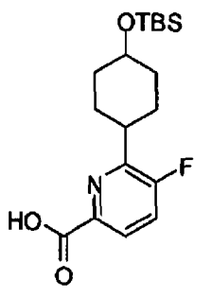
64

Synthesis of methyl 6-(4-(tert-butyldimethylsilyloxy)cyclohexyl)-5-fluoropicolinate



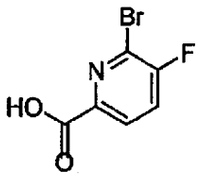
[0212] To a solution of methyl 5-fluoro-6-(4-hydroxycyclohexyl)picolinate (1.0 equiv.) in DMF (0.15 M) was added imidazole (4.0 equiv.) and TBDMSCl (2.5 equiv.). The reaction mixture was stirred at room temperature for 2 days, then added to ethyl acetate, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give methyl 6-(4-(tert-butyldimethylsilyloxy)cyclohexyl)-5-fluoropicolinate in 97% yield as a mixture of isomers (3:1). LC/MS = 368.3 (M+H), Rt = 1.4 and 1.42 min.

Synthesis of 6-(4-(tert-butyldimethylsilyloxy)cyclohexyl)-5-fluoropicolinic acid



[0213] To a solution of methyl 6-(4-(tert-butyldimethylsilyloxy)cyclohexyl)-5-fluoropicolinate (1.0 equiv.) in THF/MeOH (2:1, 0.09 M) was added LiOH (1.5 equiv.). The reaction mixture was stirred overnight at room temperature, then 1N HCl and ethyl acetate were added, the organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 6-(4-(tert-butyldimethylsilyloxy)cyclohexyl)-5-fluoropicolinic acid as a mixture of isomers (3:1) in 82% yield. LC/MS = 354.2 (M+H), Rt = 1.38 and 1.41 min.

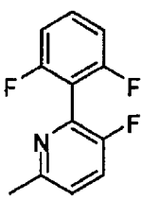
Synthesis of 6-bromo-5-fluoropicolinic acid



[0214] To 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) in H_2O (30 mL) was added potassium permanganate (1.0 equiv.). The solution was heated at 100 °C for 5 hours at which time more potassium permanganate (1.0 equiv.) was added. After heating for an additional 48 hours the material was filtered through celite (4cm x 2 inches) and rinsed with H_2O (150 mL). The combined aqueous was acidified with 1N HCl to pH=4, extracted with ethyl acetate (200 mL), washed with NaCl(sat.), dried over $MgSO_4$, filtered and concentrated to yield 6-bromo-5-fluoropicolinic acid (17%) as a white solid. LCMS (m/z): 221.9 (MH+); LC Rt = 2.05 min.

Method 4

Synthesis of 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine

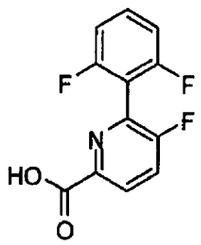


[0215] To a solution of 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) in THF and Water (10:1, 0.2 M) was added 2,6-difluorophenylboronic acid (2.0 equiv.) and potassium fluoride (3.3 equiv.). The reaction was degassed for 10 minutes, then $Pd_2(dba)_3$ (0.05 equiv.) was added, followed by tri-t-butylphosphine (0.1 equiv.). The reaction was stirred to 60 °C for 1 hour at which point, all starting material was consumed as indicated by LC/MS. The reaction was allowed to cool to room temperature, partitioned with ethyl acetate and water, the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material was diluted in EtOH to 0.1 M, and 0.5 equiv. of $NaBH_4$ was added to reduce the dba. The reaction was stirred for one hour at room temperature, then quenched with water and concentrated under vacuo to remove the ethanol. The product was extracted in ether, washed with brine, the organics were dried over sodium sulfate, filtered, and concentrated. The crude material was loaded on silica

gel and purified via column chromatography (ISCO) eluting with hexanes and ethyl acetate (0%-10% ethyl acetate). The pure fractions were combined, and concentrated to yield 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine as a light yellow oil in 86% yield. LC/MS = 224.0 (M+H), Rt = 0.84 min.

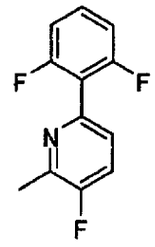
Method 5

Synthesis of 6-(2,6-difluorophenyl)-5-fluoropicolinic acid



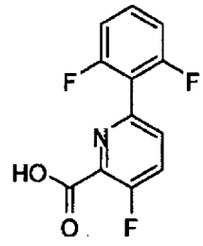
[0216] To a solution of 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine (1.0 equiv.) in water (0.05 M) was added $KMnO_4$ (2.0 equiv.) and the reaction was heated to reflux overnight. Another 2.0 equiv. of $KMnO_4$ were added and stirred at reflux for another 8 hours. The solution was cooled to room temperature, filtered through Celite and washed with water. The filtrate was acidified with 6N HCl to pH =3, the white precipitate was filtered. The filtrate was further acidified to pH = 1 and filtered again. The filtrate was extracted with ethyl acetate until no more product in the aqueous layer. The organic phase was washed with brine and dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in ethyl acetate, washed with 1N NaOH, the aqueous layer was acidified to pH=1 and the white crystals were filtered. The combined products yielded 6-(2,6-difluorophenyl)-5-fluoropicolinic acid in 32% yield as a white solid. LC/MS = 254.0 (M+H), Rt = 0.71 min.

Synthesis of 6-(2,6-difluorophenyl)-3-fluoro-2-methylpyridine



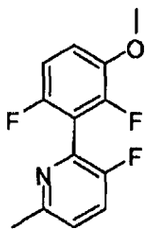
[0217] To a solution of 6-bromo-3-fluoro-2-methylpyridine (1.0 equiv.) in ethanol and toluene (1:1, 0.2 M) was added 2,6-difluorophenylboronic acid, DIEA (5 equiv.) and $Pd(PPh_3)_4$ (0.2 equiv.). The reaction was heated in the microwave at 120 °C for 30 min. The solution was filtered and rinsed with ethyl acetate. The volatiles were removed in vacuo and the crude was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (2.5-20% ethyl acetate). Upon concentration of the pure fractions, 6-(2,6-difluorophenyl)-3-fluoro-2-methylpyridine was isolated in 88% yield. LC/MS = 224.1 (M+H), Rt = 0.87 min.

Synthesis of 6-(2,6-difluorophenyl)-3-fluoropicolinic acid



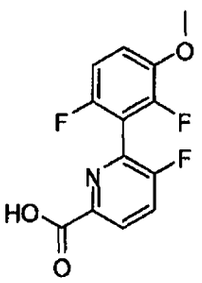
[0218] Method 5 was followed using 6-(2,6-difluorophenyl)-3-fluoro-2-methylpyridine (1.0 equiv.) and potassium permanganate (6.0 equiv.) to give 6-(2,6-difluorophenyl)-3-fluoropicolinic acid in 30% yield. LC/MS = 254.1 (M+H), Rt = 0.70 min.

Synthesis of 2-(2,6-difluoro-3-methoxyphenyl)-3-fluoro-6-methylpyridine



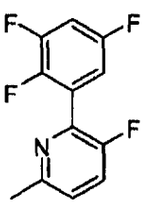
[0219] Method 4 was followed using 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) and 2,6-difluoro-3-methoxyphenylboronic acid (2.0 equiv.) to give 2-(2,6-difluoro-3-methoxyphenyl)-3-fluoro-6-methylpyridine in 60% yield. LC/MS = 254.1 (M+H), Rt = 0.85 min.

Synthesis of 6-(2,6-difluoro-3-methoxyphenyl)-5-fluoropicolinic acid



[0220] Method 5 was followed using 2-(2,6-difluoro-3-methoxyphenyl)-3-fluoro-6-methylpyridine (1.0 equiv.) and potassium permanganate (4.0 equiv.) to give 6-(2,6-difluoro-3-methoxyphenyl)-5-fluoropicolinic acid in 27% yield. LC/MS = 284.1 (M+H), Rt = 0.75 min.

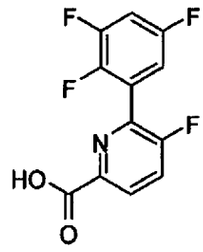
Synthesis of 3-fluoro-6-methyl-2-(2,3,5-trifluorophenyl)pyridine



[0221] To a solution of 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) in dioxane (0.2 M) was added 2,3,5-trifluorophenylboronic acid and Pd(dppf)Cl_2-DCM (0.1 equiv.). Aqueous sodium carbonate (2M solution, 2.0 equiv.) was added and the reaction was heated in the microwave at 120 °C for 15 min. The solution was partitioned between

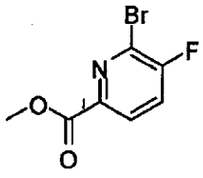
ethyl acetate and sat. $NaHCO_3$, the organic phase was washed with brine, dried with magnesium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:3) to give 3-fluoro-6-methyl-2-(2,3,5-trifluorophenyl)pyridine in 87% yield. LC/MS = 242.1 (M+H), Rt = 0.98 min.

Synthesis of 5-fluoro-6-(2,3,5-trifluorophenyl)picolinic acid



[0222] To a solution of 3-fluoro-6-methyl-2-(2,3,5-trifluorophenyl)pyridine (1.0 equiv.) in water and t-BuOH (2:1, 0.06 M) was added potassium permanganate (10 equiv.) and the solution was heated at 90 °C for 5 hours. Upon cooling to room temperature, the solution was filtered, and the filtrate was concentrated under reduced pressure to yield 5-fluoro-6-(2,3,5-trifluorophenyl)picolinic acid in 89% yield. LC/MS = 272.0 (M+H), Rt = 0.80 min.

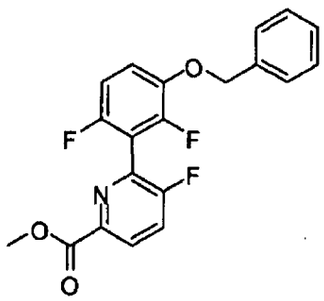
Synthesis of methyl 6-bromo-5-fluoropicolinate



[0223] To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in methanol (0.2 M) was added H_2SO_4 (4.2 equiv.) and the reaction was stirred at room temperature for two hours. Upon completion of the reaction as monitored by LC/MS, the reaction was diluted with ethyl acetate and quenched slowly with saturated aqueous $NaHCO_3$. The reaction was poured into a separatory funnel and extracted with ethyl acetate. The organic phase was dried with magnesium sulfate, filtered, and concentrated in vacuo to provide methyl 6-bromo-5-fluoropicolinate as a white solid (>99%). LC/MS = 233.9/235.9 (M+H), Rt = 0.69 min.

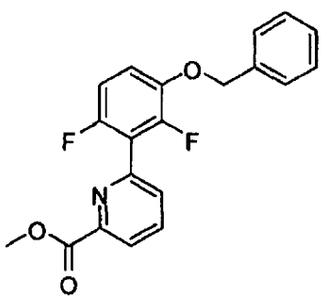
Method 6

Synthesis of methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)-5-fluoropicolinate



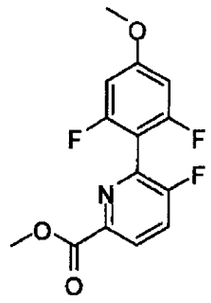
[0224] To a solution of methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) in THF and water (10:1, 0.1 M) was added 3-(benzyloxy)-2,6-difluorophenylboronic acid (2.5 equiv.) and potassium fluoride (3.3 equiv.). The reaction was degassed with nitrogen, then $Pd_2(dba)_3$ (0.25 equiv.) and tri-tert-butylphosphine (0.5 equiv.) were added and the reaction was heated to 80 °C for one hour. LC/MS analysis indicated complete conversion of the starting material to product. The reaction was cooled to room temperature, then concentrated in vacuo and fused to silica gel. The crude product was purified by ISCO flash chromatography eluting with ethyl acetate and hexanes (0% to 30% ethyl acetate) to provide methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)-5-fluoropicolinate as the desired product as a light yellow oil in 96% yield. LC/MS = 374.0 (M+H), Rt = 1.07 min.

Synthesis of methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)picolinate



[0225] Method 6 was followed using methyl 6-bromopicolinate (1.0 equiv.) and 3-(benzyloxy)-2,6-difluorophenylboronic acid (2.5 equiv.) to give methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)picolinate as a light yellow solid in 95% yield. LC/MS = 356.2 (M+H), Rt = 1.03 min.

Synthesis of methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate



[0226] Method 6 was followed using methyl 6-bromopicolinate (1.0 equiv.) and 2,6-difluoro-4-methoxyphenylboronic acid (2.5 equiv.) to give methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate as a white solid in 85% yield. LC/MS = 298.0 (M+H), Rt = 0.89 min.

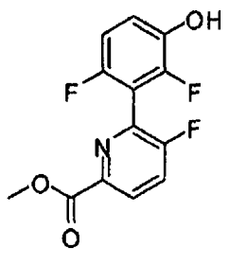
Synthesis of 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid



[0227] To a solution of methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate (1.0 equiv.) in THF/MeOH (2:1, 0.09 M) was added LiOH (1.5 equiv.) and the reaction was stirred at room temperature for 1 hour. The solution was quenched with 1N HCl, extracted with ethyl acetate, washed with brine, dried with sodium sulfate, filtered and concentrated to give 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid in 84% yield. LC/MS = 284.1 (M+H), Rt = 0.76 min.

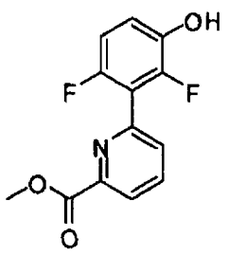
Method 7

Synthesis of methyl 6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinate



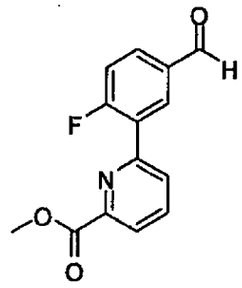
[0228] To a solution of methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)-5-fluoropicolinate (1.0 equiv.) in methanol (0.1 M) was added 10% Pd/C (0.1 equiv.) in ethyl acetate. The reaction was placed under an atmosphere of hydrogen and stirred for 2 hours. Upon completion, the solution was filtered over a pad of Celite, the pad was washed with methanol, the filtrate was concentrated *in vacuo* to give methyl 6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinate as a grey oil in 86% yield. LC/MS = 284.0 (M+H), Rt = 0.90 min.

Synthesis of methyl 6-(2,6-difluoro-3-hydroxyphenyl)picolinate



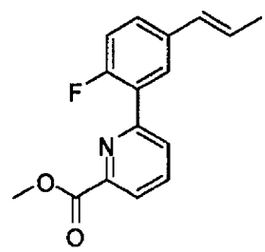
[0229] Method 7 was followed using methyl 6-(3-(benzyloxy)-2,6-difluorophenyl)picolinate (1.0 equiv.) to yield methyl 6-(2,6-difluoro-3-hydroxyphenyl)picolinate as a light brown solid in 96% yield. LC/MS = 266.0 (M+H), Rt = 0.68 min.

Synthesis of methyl 6-(2-fluoro-5-formylphenyl)picolinate



[0230] To a solution of methyl 6-bromopicolinate (1.0 equiv.) in DME (0.03 M) in a microwave vial was added Pd(dppf)Cl_2-DCM (0.05 equiv.), 2-fluoro-5-formylphenylboronic acid (1.5 equiv.) and 2M Na_2CO_3 (2 equiv.). The reagents were heated to 120 °C for 20 min. A mixture of the desired product and the corresponding carboxylic acid was detected by LC/MS, the reaction was diluted with ethyl acetate, washed with HCl (pH=5), the acidic phase was extracted with ethyl acetate, the combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo to provide a light brown solid. The solid was dissolved in MeOH and treated with 3 equiv. of TMS-diazomethane at room temperature. Upon complete conversion of the carboxylic acid to the corresponding methyl ester, the reaction was concentrated in vacuo and the crude material was purified via silica gel column chromatography (ISCO) eluting with 30% ethyl acetate in hexanes to provide methyl 6-(2-fluoro-5-formylphenyl)picolinate as a yellow solid in 58% yield. LC/MS = 260.0 (M+H), Rt = 0.70 min.

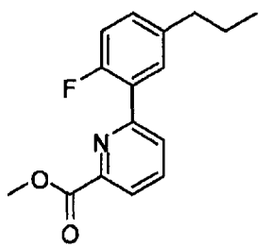
Synthesis of (E)-methyl 6-(2-fluoro-5-(prop-1-enyl)phenyl)picolinate



[0231] To a solution of methyl 6-(2-fluoro-5-formylphenyl)picolinate (1.0 equiv.) in MeOH (0.17 M) was added ethyltriphenylphosphonium bromide (1.0 equiv.) followed by sodium methoxide (1.5 equiv.). The reaction was heated to 65 °C for 5 hours, then cooled to room temperature and concentrated in vacuo. The crude material was purified via silica gel column chromatography (ISCO) eluting with 50% ethyl acetate

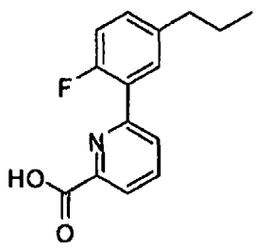
in hexanes to provide (E)-methyl 6-(2-fluoro-5-(prop-1-enyl)phenyl)picolinate as a white solid in 81% yield. LC/MS = 272.0 (M+H), Rt = 0.73 min.

Synthesis of methyl 6-(2-fluoro-5-propylphenyl)picolinate



[0232] To a solution of (E)-methyl 6-(2-fluoro-5-(prop-1-enyl)phenyl)-picolinate (1.0 equiv.) in MeOH (0.04 M) was 10% Pd/C (0.5 equiv.) and the reaction was placed under an atmosphere of hydrogen and left stirring overnight. The mixture was filtered over a pad of Celite and washed with MeOH. The filtrate was concentrated in vacuo to provide methyl 6-(2-fluoro-5-propylphenyl)picolinate as a light grey oil in 97% yield. LC/MS = 274.2 (M+H), Rt = 0.61 min.

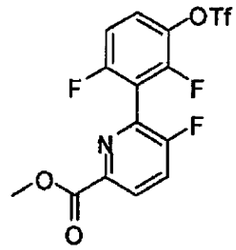
Synthesis of 6-(2-fluoro-5-propylphenyl)picolinic acid



[0233] To a solution of methyl 6-(2-fluoro-5-propylphenyl)picolinate (1.0 equiv.) in THF was added lithium hydroxide (10 equiv.) and the reaction was stirred at room temperature for 1 hour. The THF solvent was removed in vacuo and the remaining basic phase was acidified with concentrated HCl. The aqueous layer was extracted with ethyl acetate (2x), the organic phase was dried with sodium sulfate, filtered and concentrated to give 6-(2-fluoro-5-propylphenyl)picolinic acid in 35% yield. LC/MS = 260.2 (M+H), Rt = 0.36 min.

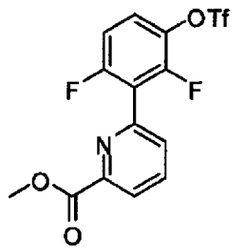
Method 8

Synthesis of methyl 6-(2,6-difluoro-3-(trifluoromethyl-sulfonyloxy)phenyl)-5-fluoropicolinate



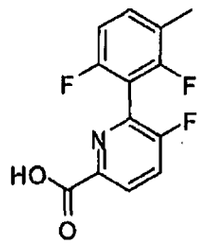
[0234] To a solution of methyl 6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinate (1.0 equiv.) in DCM (0.2 M) was added DIEA (2.0 equiv.) and 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.5 equiv.). The reaction was allowed to stir overnight at room temperature. The solution was quenched with water, the organic phase was dried with sodium sulfate, and concentrated. The crude material was purified via ISCO chromatography eluting with ethyl acetate and hexanes (0-30% ethyl acetate). The pure fractions were concentrated to give methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)phenyl)-5-fluoropicolinate as the desired product as a clear oil in 68% yield. LC/MS = 416.1 (M+H), Rt = 1.08 min.

Synthesis of methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)-phenyl)picolinate



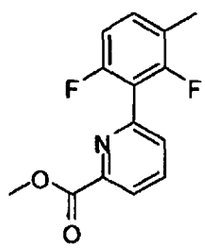
[0235] Method 8 was followed using methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)phenyl)-5-fluoropicolinate (1.0 equiv.) to yield methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)phenyl)picolinate as a colorless oil in >99% yield. LC/MS = 397.9 (M+H), Rt = 1.03 min.

Synthesis of 6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinic acid



[0236] To a solution methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy) phenyl)-5-fluoropicolinate (1.0 equiv.) in dioxane and water (10:1, 0.15 M) was added methyl boronic acid (3.0 equiv.) and potassium carbonate (3.0 equiv.). The reaction was degassed with nitrogen for 10 min, then $Pd(PPh_3)_4$ (0.1 equiv.) was added to the solution and heated to 100 °C for 3 hours. LC/MS of the reaction at this point indicated complete conversion to the carboxylic acid product (M+H = 268). Cooled to room temperature and added water and ethyl acetate. The two layers were separated, the aqueous phase was acidified with concentrated HCl to pH =1 and extracted with ethyl acetate. The organic phase was dried with sodium sulfate, filtered, and concentrated under vacuo to give 6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinic acid as a clear oil in 97% yield. LC/MS = 268.1 (M+H), Rt = 0.82 min.

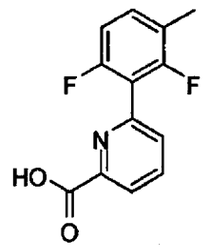
Synthesis of methyl 6-(2,6-difluoro-3-methylphenyl)picolinate



[0237] To a solution of methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)-phenyl)picolinate (1.0 equiv.) in toluene was added $Pd(dppf)Cl_2$-DCM (0.1 equiv.) followed by dimethyl zinc (3 .0 equiv.). The solution turned from orange to bright yellow. The reaction was heated to 80 °C for 2 hours at which time, LC/MS analysis indicated complete conversion to product. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with brine. The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo* to provide methyl 6-(2,6-difluoro-

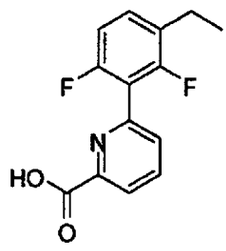
3-methylphenyl)picolinate as a brown oil in quantitative yield. LC/MS = 264.0 (M+H), Rt = 0.90 min.

Synthesis of 6-(2,6-difluoro-3-methylphenyl)picolinic acid



[0238] To a solution of methyl 6-(2,6-difluoro-3-methylphenyl)picolinate (1.0 equiv.) in THF was added sodium hydroxide (10 equiv.) and the reaction was stirred for 2 hours. The solution was diluted with ethyl acetate and washed with 1N NaOH (2x). The combined basic aqueous washes were combined and acidified with concentrated HCl. The acidic aqueous phase was extracted with ethyl acetate (2x), the combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo to provide 6-(2,6-difluoro-3-methylphenyl)picolinic acid as a white solid in 85% yield. LC/MS = 250.0 (M+H), Rt = 0.76 min.

Synthesis of 6-(3-ethyl-2,6-difluorophenyl)picolinic acid



[0239] To a solution of methyl 6-(2,6-difluoro-3-(trifluoromethylsulfonyloxy)-phenyl)picolinate (1.0 equiv.) in toluene (0.15 M) was added Pd(dppf)Cl_2-DCM (0.1 equiv.) followed by diethyl zinc (3 .0 equiv.). The solution turned from orange to bright yellow. The reaction was heated to 70 °C for 2 hours at which time, LC/MS analysis indicated a mixture of 1:3:1 ratio of hydrolyzed product, desired product and unknown by-product. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with 1N NaOH (2x). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to provide a brown oil. The oil was redissolved in

THF and treated with 1N NaOH for one hour. The reaction was then diluted with ethyl acetate and washed with 1N NaOH (2x). The basic washings were combined, acidified with concentrated HCl and extracted with ethyl acetate (3x). The organic phase was dried with magnesium sulfate, filtered, and concentrated in vacuo to provide 6-(3-ethyl-2,6-difluorophenyl)picolinic acid as a light brown oil in >99% yield. LC/MS = 264.1 (M+H), Rt = 0.88 min.

Method 9

[0240] A homogeneous solution of 1 eq each of amine, carboxylic acid, HOAT and EDC in DMF, at a concentration of 0.5 M, was left standing for 24 hours at which time water and ethyl acetate were added. The organic phase was dried with sodium sulfate and purified via silica gel column chromatography eluting with ethyl acetate and hexanes to give the desired protected amide product. Alternatively the crude reaction mixture was directly purified by HPLC. Upon lyophilization, the TFA salt of the protected amide product was obtained. Alternatively, the HPLC fractions could be added to EtOAc and solid Na_2CO_3, separated and washed with $NaCl_{(sat.)}$. Upon drying over $MgSO_4$, filtering and removing the volatiles *in vacuo*, the protected amide product was obtained as a free base. Alternatively, the crude reaction mixture was used for the deprotection step without further purification.

[0241] If an N-Boc protected amine was present, it was removed by treating with excess 4M HCl/ dioxane for 14 hours or by treating with 25% TFA/CH_2Cl_2 for 2 hours. Upon removal of the volatiles *in vacuo*, the material was purified by RP HPLC yielding after lyophilization the amide product as the TFA salt. Alternatively, the HPLC fractions could be added to EtOAc and solid Na_2CO_3, separated and washed with $NaCl_{(sat.)}$. Upon drying over $MgSO_4$, filtering and removing the volatiles *in vacuo* the free base was obtained. Upon dissolving in MeCN/H_2O, adding 1 eq. of 1 N HCl and lyophilizing, the HCl salt of the amide product was obtained.

[0242] If an N-Boc1,2 amino alcohol cyclic carbamate was present, prior to Boc deprotection the cyclic carbamate could be cleaved by treating with Cs_2CO_3 (0.5 eq) in ethanol at a concentration of 0.1 M for three hours. After removal of volatiles *in vacuo*, the Boc amino group was deprotected as described above.

[0243] If an N-Boc, OAc group were present, prior to Boc deprotection, the acetate group could be cleaved by treating with K_2CO_3 (2.0 equiv.) in ethanol at a concentration of 0.1 M for 24 hours.

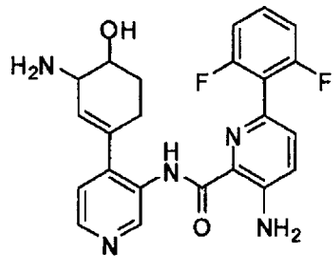
[0244] If an N-phthalimide group was present, the amine was deprotected by treating with hydrazine in MeOH at 65°C for three hours. Upon cooling and filtering off the white precipitate, the filtrate was concentrated and purified by RP HPLC to yield the amino amide product.

[0245] If a TBDMS ether was present, it was deprotected prior to Boc removal by treating with 6N HCl, THF, methanol (1:2:1) at room temperature for 12 h. After removal of volatiles *in vacuo*, the Boc amino group was deprotected as described above. Alternatively, the TBDMS ether and Boc group could be both deprotected with 6N HCl, THF, methanol (1:2:1) if left at rt for 24 hours, or heated at 60 °C for 3 hours.

[0246] If a OMe group was present, it was deprotected by treating with 1 M BBr_3 in DCM (2.0 equiv.) for 24 hours. Water was added dropwise and the volatiles were removed *in vacuo*. The material was purified via reverse phase HPLC as described above.

[0247] If a OBn group was present, it was deprotected by treatment with 10% Pd/C (0.2 equiv.) under an atmosphere of hydrogen in ethyl acetate and methanol (1:2). Upon completion, the reaction was filtered through Celite, washed with methanol, and the filtrate was concentrated *in vacuo*.

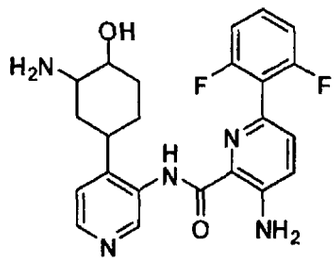
Synthesis of (+/-)-3-amino-N-(4-(3-amino-4-hydroxycyclohex-1-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide



[0248] Following Method 9, (+/-)-tert-butyl 3-(3-aminopyridin-4-yl)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enylcarbamate and 3-amino-6-(2,6-difluorophenyl)-picolinic acid were coupled and deprotected to yield (+/-)-3-amino-N-(4-(3-amino-4-

hydroxycyclohex-1-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide as the TFA salt. LCMS (*m/z*): 438.2 (MH^+), LC R_t = 2.00 min.

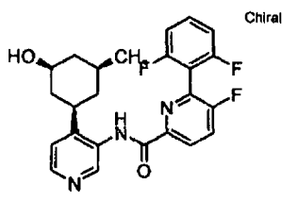
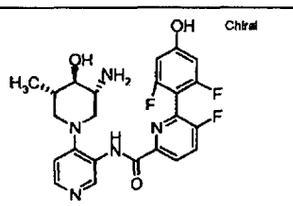
Synthesis of (+/-)-3-amino-N-(4-(3-amino-4-hydroxycyclohexyl)-pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide

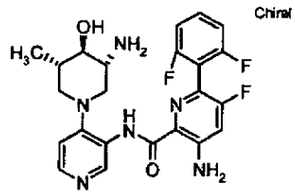
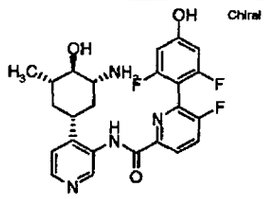
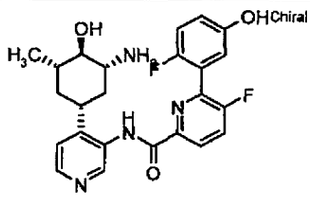
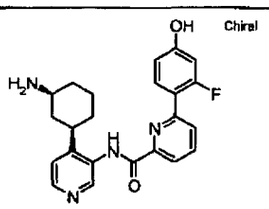
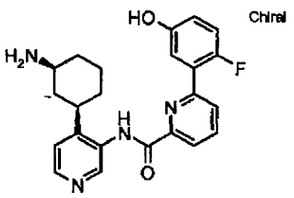
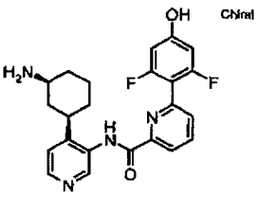
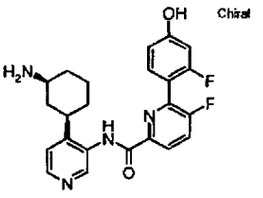


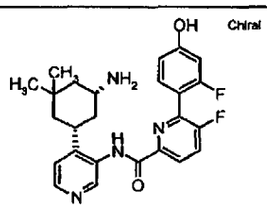
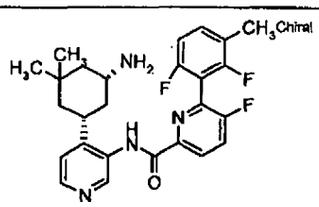
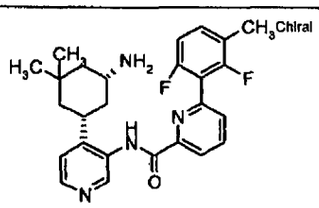
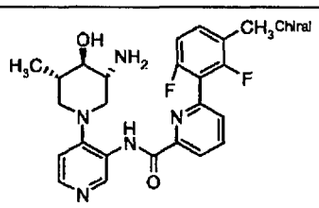
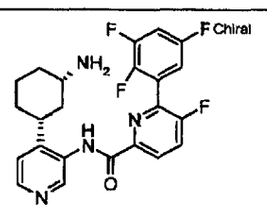
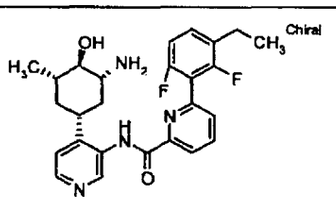
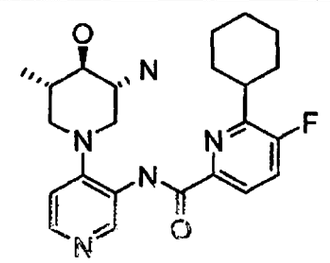
[0249] Following Method 9, (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-2-(tert-butyldimethylsilyloxy)cyclohexylcarbamate and 3-amino-6-(2,6-difluorophenyl)picolinic acid were coupled and deprotected to yield (+/-)-3-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide as the TFA salt in 18% yield. LCMS (*m/z*): 440.3 (MH^+), LC R_t = 2.04 min.

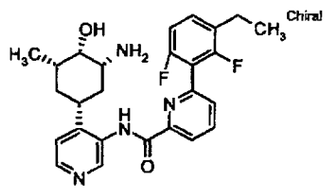
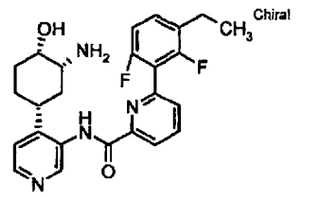
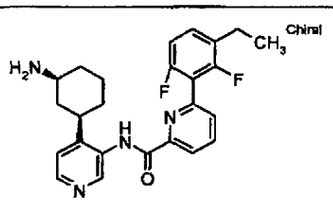
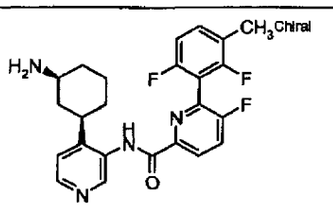
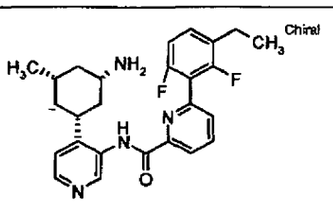
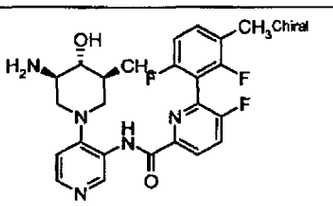
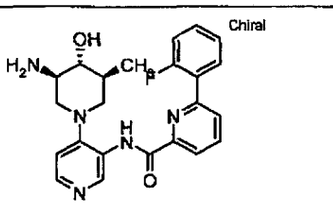
[0250] Following the procedures of Method 9, the following compounds were prepared:

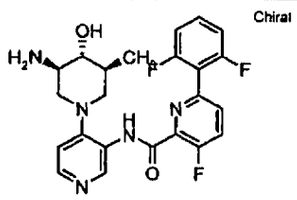
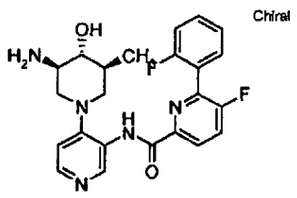
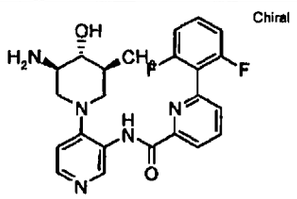
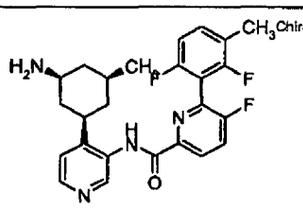
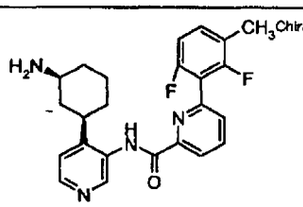
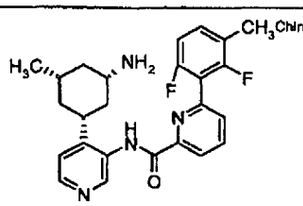
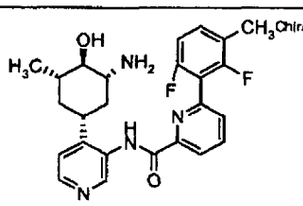
TABLE 1

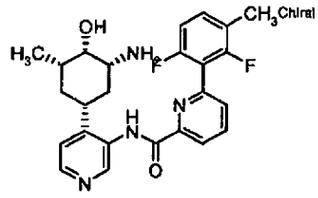
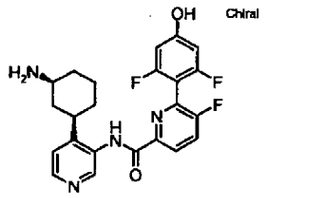
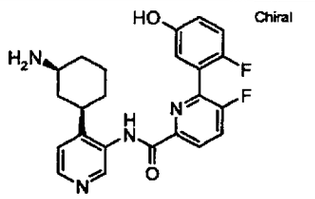
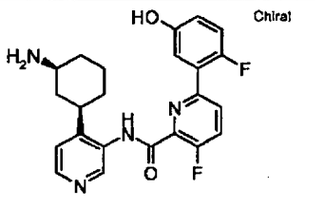
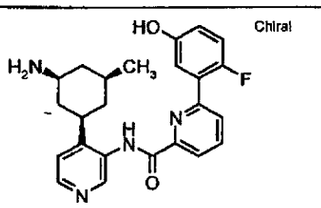
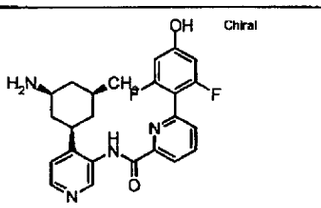
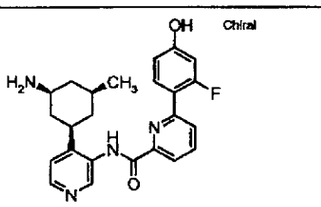
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
1		442.2	0.75	6-(2,6-difluorophenyl)-5-fluoro-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)picolinamide
2		474.3	0.52	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide

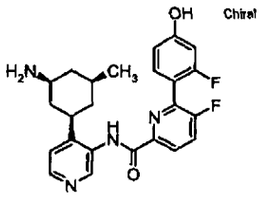
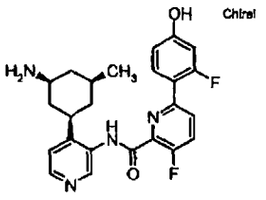
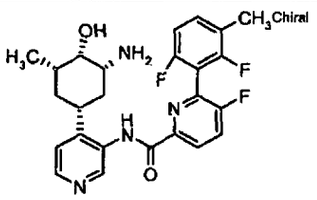
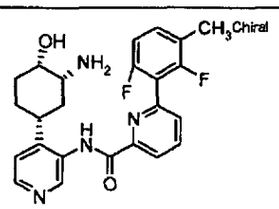
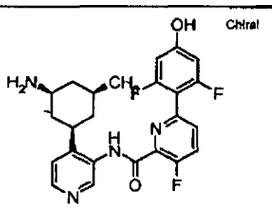
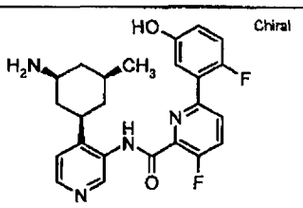
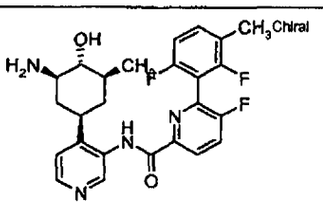
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
3		473.3	0.55	3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
4		473.3	0.52	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide
5		455.3	0.55	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-hydroxyphenyl)picolinamide
6		407.2	0.52	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2-fluoro-4-hydroxyphenyl)picolinamide
7		407.2	0.53	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-hydroxyphenyl)picolinamide
8		425.2	0.54	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)picolinamide
9		425.2	0.53	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-4-hydroxyphenyl)picolinamide

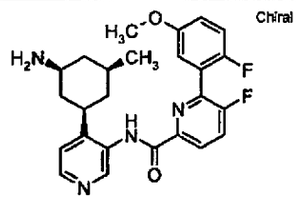
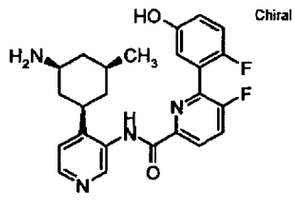
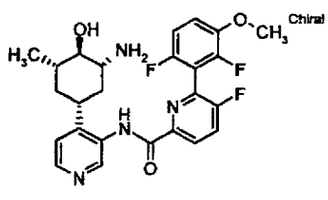
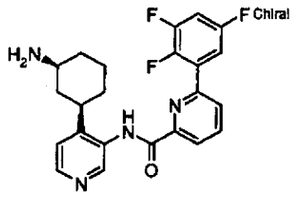
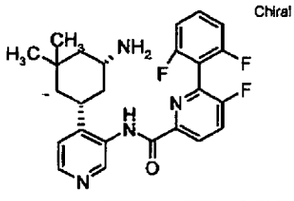
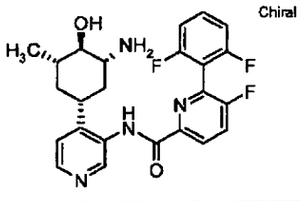
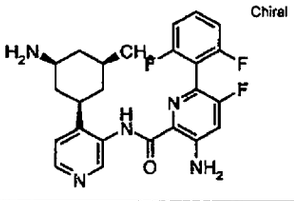
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
10		453.3	0.58	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-4-hydroxyphenyl)picolinamide
11		469.2	0.7	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide
12		451.1	0.69	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
13		454.2	0.58	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
14		445.2	0.62	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-5-fluoro-6-(2,3,5-trifluorophenyl)picolinamide
15		467.5	0.63	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(3-ethyl-2,6-difluorophenyl)picolinamide
16		428.2	0.63	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-cyclohexyl-5-fluoropicolinamide

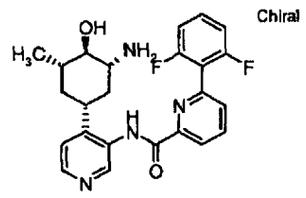
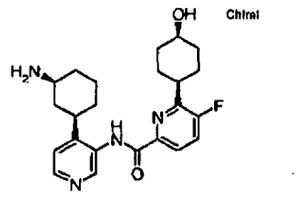
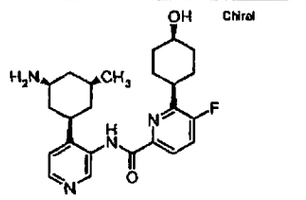
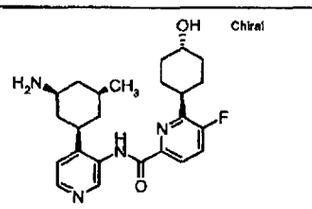
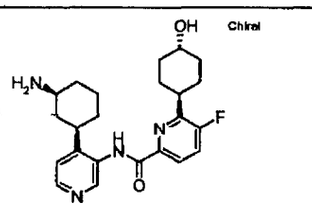
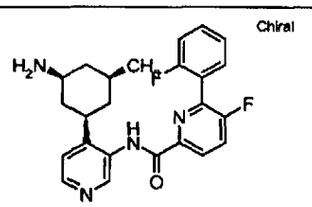
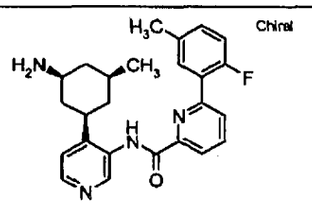
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
17		467.3	0.64	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(3-ethyl-2,6-difluorophenyl)picolinamide
18		453.2	0.66	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(3-ethyl-2,6-difluorophenyl)picolinamide
19		437.2	0.67	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(3-ethyl-2,6-difluorophenyl)picolinamide
20		441.2	0.64	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide
21		451.2	0.7	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(3-ethyl-2,6-difluorophenyl)picolinamide
22		472.3	0.59	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide
23		422.3	0.53	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2-fluorophenyl)picolinamide

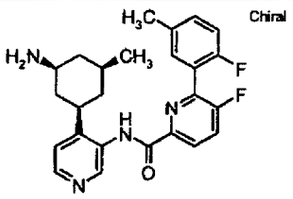
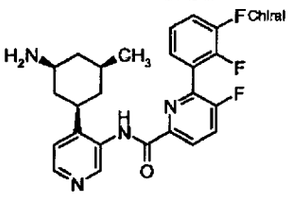
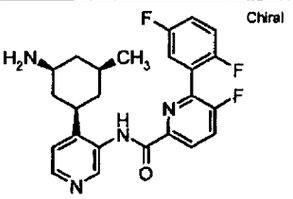
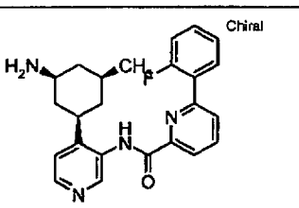
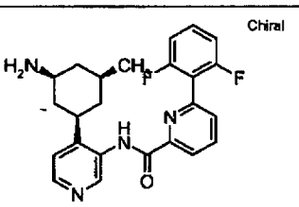
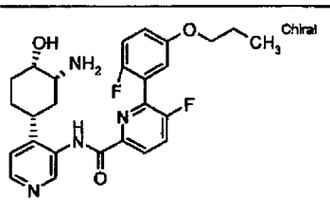
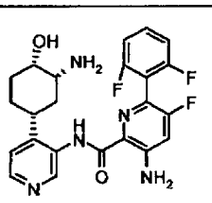
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
24		458.3	0.51	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-3-fluoropicolinamide
25		440.3	0.54	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
26		440.2	0.53	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
27		455.3	0.66	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide
28		423.2	0.61	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
29		437.2	0.64	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
30		453.2	0.59	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide

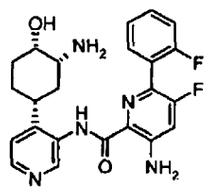
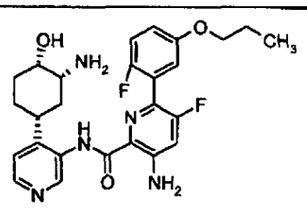
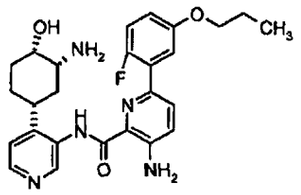
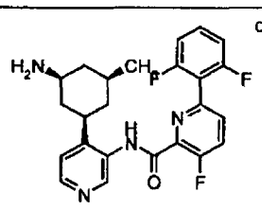
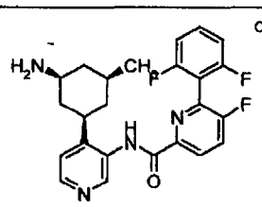
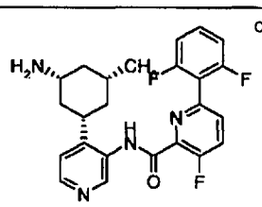
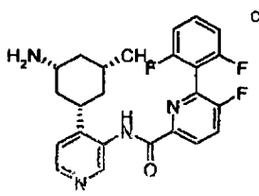
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
31		453.2	0.6	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
32		443.2	0.55	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide
33		425.2	0.53	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-hydroxyphenyl)picolinamide
34		425.2	0.52	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-3-fluoro-6-(2-fluoro-5-hydroxyphenyl)picolinamide
35		421.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-hydroxyphenyl)picolinamide
36		439.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)picolinamide
37		421.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2-fluoro-4-hydroxyphenyl)picolinamide

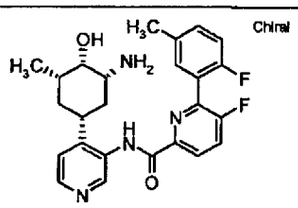
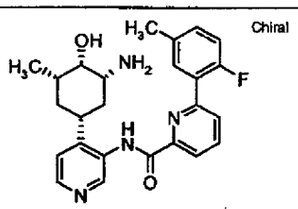
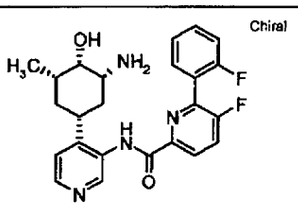
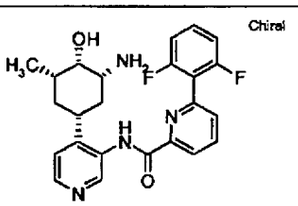
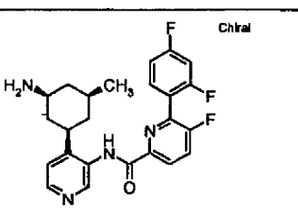
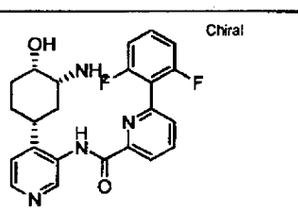
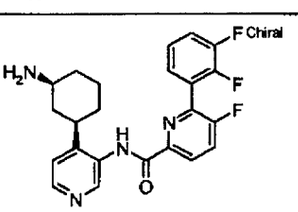
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
38		439.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-4-hydroxyphenyl)picolinamide
39		439.2	0.55	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-3-fluoro-6-(2-fluoro-4-hydroxyphenyl)picolinamide
40		471.2	0.62	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide
41		439.2	0.57	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)picolinamide
42		457.2	0.56	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-3-fluoropicolinamide
43		439.2	0.56	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-3-fluoro-6-(2-fluoro-5-hydroxyphenyl)picolinamide
44		471.2	0.62	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide

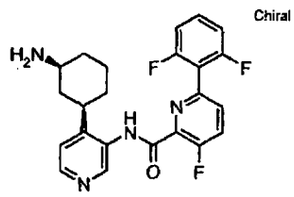
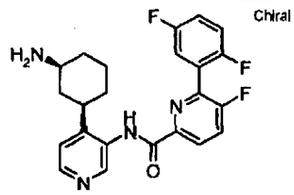
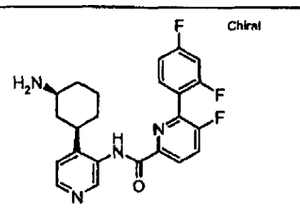
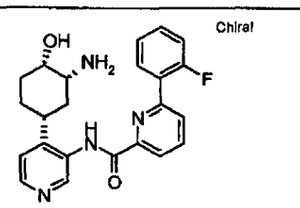
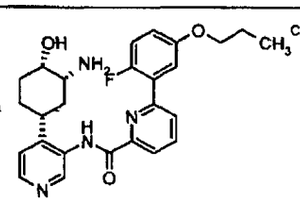
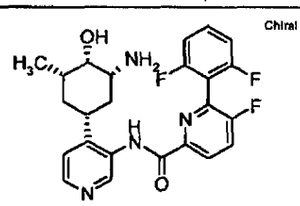
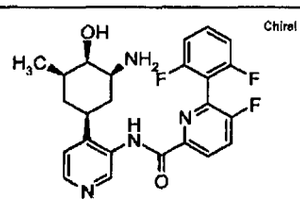
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
45		453.1	0.61	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-methoxyphenyl)picolinamide
46		439.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-hydroxyphenyl)picolinamide
47		487.1		N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-methoxyphenyl)-5-fluoropicolinamide
48		427.2	0.59	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,3,5-trifluorophenyl)picolinamide
49		455.2	0.63	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
50		457.2	0.58	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
51		456.1	0.58	3-amino-N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

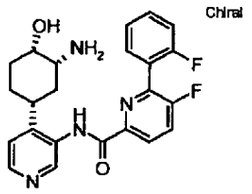
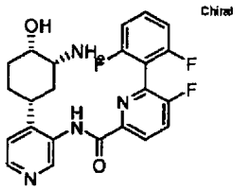
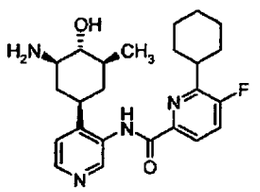
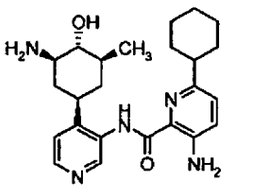
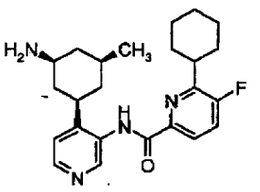
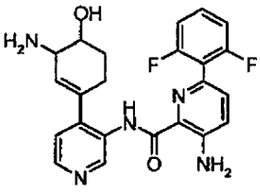
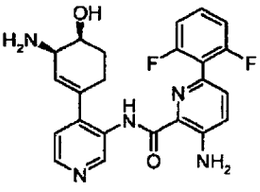
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
52		439.1	0.68	N-(4-((1S,3S,4S,5R)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
53		413.3	0.55	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-5-fluoro-6-((1s,4s)-4-hydroxycyclohexyl)picolinamide
54		427.3	0.59	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-((1s,4s)-4-hydroxycyclohexyl)picolinamide
55		427.3	0.55	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-((1r,4r)-4-hydroxycyclohexyl)picolinamide
56		413.3	0.48	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-5-fluoro-6-((1r,4r)-4-hydroxycyclohexyl)picolinamide
57		423.3	0.64	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
58		419.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-methylphenyl)picolinamide

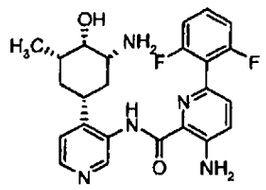
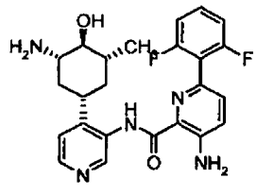
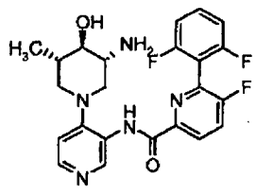
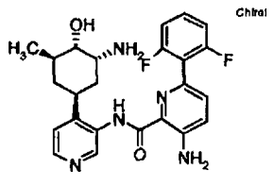
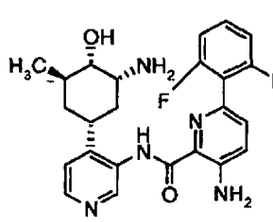
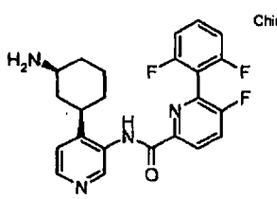
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
59		437.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-methylphenyl)picolinamide
60		441.2	0.70	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide
61		441.2	0.68	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide
62		405.2	0.67	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2-fluorophenyl)picolinamide
63		423.2	0.65	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
64		483.2	0.66	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinamide
65		458.1	0.55	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

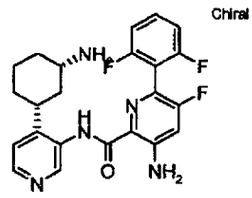
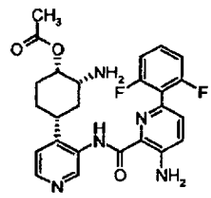
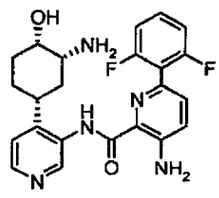
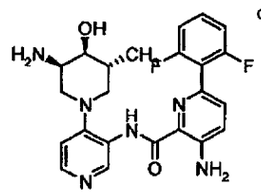
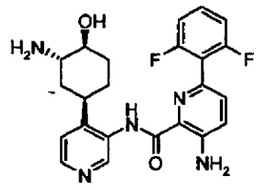
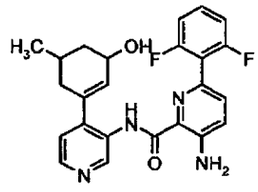
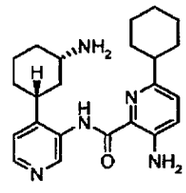
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
66		440.1	0.55	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
67		498.2	0.66	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-propoxyphenyl)picolinamide
68		480.2	0.65	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-propoxyphenyl)picolinamide
69		441.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-3-fluoropicolinamide
70		441.3	0.70	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
71		441.3	0.66	N-(4-((1S,3R,5R)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-3-fluoropicolinamide
72		441.3	0.70	N-(4-((1S,3R,5R)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

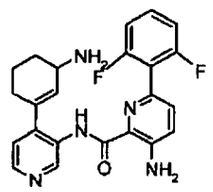
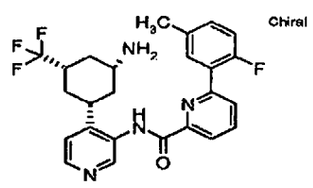
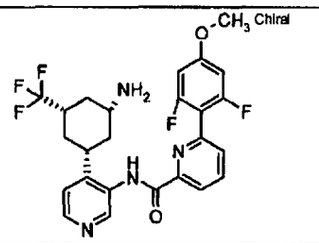
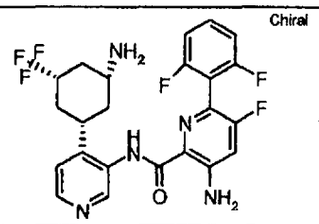
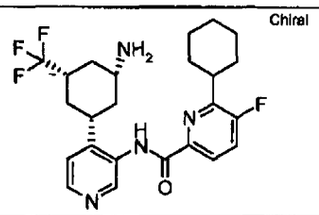
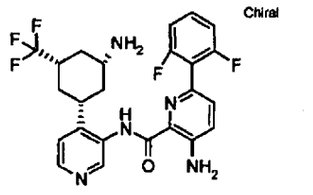
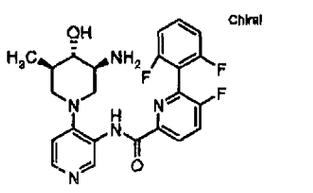
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
73		453.1	0.7	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-methylphenyl)picolinamide
74		435.0	0.6	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-methylphenyl)picolinamide
75		439.2	0.57	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
76		439.2	0.55	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
77		441.3	0.62	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,4-difluorophenyl)-5-fluoropicolinamide
78		425.2	0.52	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
79		427.2	0.58	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide

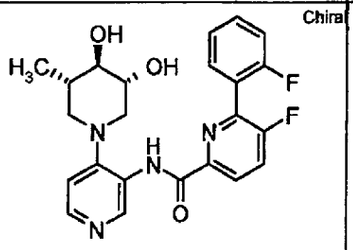
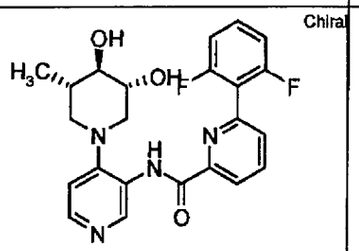
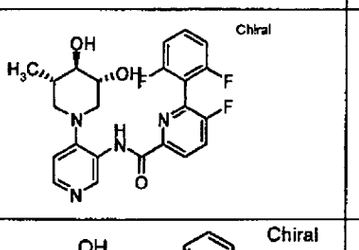
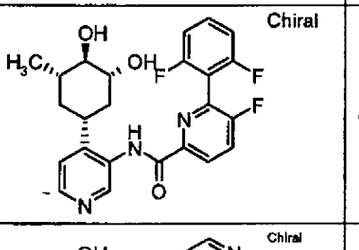
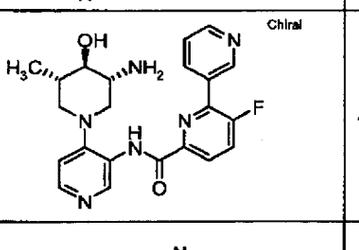
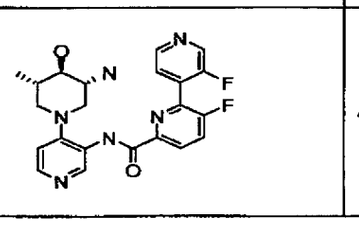
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
80		427.2	0.54	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-3-fluoropicolinamide
81		427.2	0.57	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide
82		427.2	0.58	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,4-difluorophenyl)-5-fluoropicolinamide
83		407.1	0.51	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2-fluorophenyl)picolinamide
84		465.2	0.62	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-propoxyphenyl)picolinamide
85		457.2	0.56	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
86		457.0	0.56	N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

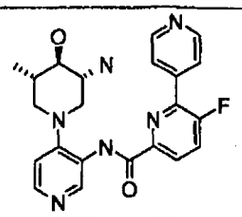
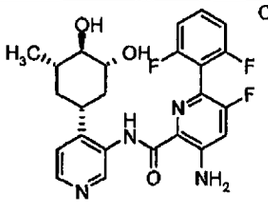
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
87		425.1	0.52	N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
88		443.0	0.53	N-(4-((1S,3S,4R)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
89		427.3	0.63	N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-cyclohexyl-5-fluoropicolinamide
90		424.3	0.6	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-cyclohexylpicolinamide
91		411.3	0.67	N-(4-(3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-cyclohexyl-5-fluoropicolinamide
92		438.3	0.51	3-amino-N-(4-(trans)-3-amino-4-hydroxycyclohex-1-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
93		438.3	0.51	3-amino-N-(4-(cis)-3-amino-4-hydroxycyclohex-1-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide

Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
94		454.1	0.54	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
95		454.3	0.54	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
96		458.1	0.54	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
97		454.1	0.55	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
98		454.1	0.54	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
99		427.2	0.55	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

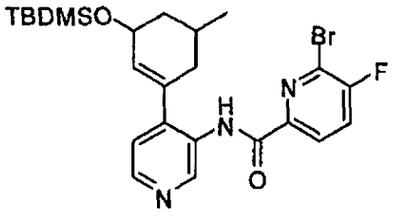
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
100	 Chiral	442.2	0.59	3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
101		482.2	0.56	2-amino-4-(3-(3-amino-6-(2,6-difluorophenyl)picolinamido)pyridin-4-yl)cyclohexyl acetate
102		440.3	0.52	3-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
103	 Chiral	455.3	0.53	3-amino-N-(4-((3R,4S,5R)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
104		440.2	0.52	3-amino-N-(4-((1R,3S,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
105		438.2	2.92	3-amino-6-(2,6-difluorophenyl)-N-(4-(3-hydroxy-5-methylcyclohex-1-enyl)pyridin-3-yl)picolinamide
106		394.3	0.74	3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-cyclohexylpicolinamide

Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
107		421.9	0.59	3-amino-N-(4-(3-aminocyclohex-1-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
108		473.3	0.67	N-(4-((1R,3R,5S)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-(2-fluoro-5-methylphenyl)picolinamide
109		507.2	0.65	N-(4-((1R,3R,5S)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-methoxyphenyl)picolinamide
110		510.2	0.64	3-amino-N-(4-((1R,3R,5S)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
111		465.3	0.72	N-(4-((1R,3R,5S)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-cyclohexyl-5-fluoropicolinamide
112		492.2	0.62	3-amino-N-(4-((1R,3R,5S)-3-amino-5-(trifluoromethyl)cyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide
113		458.2	0.55	N-(4-((3S,4S,5R)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
114		441.1	0.61	N-(4-((3R,4R,5S)-3,4-dihydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-5-fluoro-6-(2-fluorophenyl)picolinamide
115		441.1	0.6	6-(2,6-difluorophenyl)-N-(4-((3R,4R,5S)-3,4-dihydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)picolinamide
116		459.1	0.61	6-(2,6-difluorophenyl)-N-(4-((3R,4R,5S)-3,4-dihydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-5-fluoropicolinamide
117		458.2	0.62	6-(2,6-Difluorophenyl)-N-(4-((1R,3R,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoropicolinamide
118		423.2	0.32	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-3-fluoro-2,3'-bipyridine-6-carboxamide
119		441.2	0.46	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-3,3'-difluoro-2,4'-bipyridine-6-carboxamide

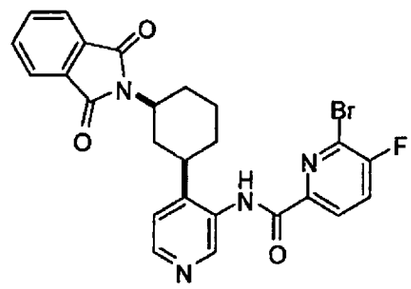
Example No.	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
120		423.1	0.3	N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-3-fluoro-2,4'-bipyridine-6-carboxamide
121	 Chiral	473.1	0.68	3-amino-6-(2,6-difluorophenyl)-N-(4-((1R,3R,4R,5S)-3,4-dihydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoropicolinamide

Synthesis of 6-bromo-N-(4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)pyridin-3-yl)-5-fluoropicolinamide



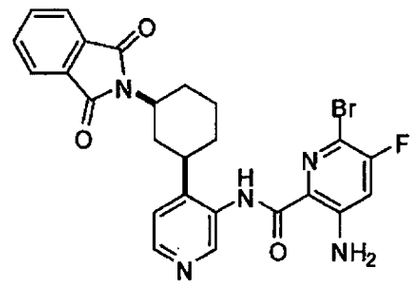
[0251] Following Method 9, 4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)pyridin-3-amine and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, 6-bromo-N-(4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)pyridin-3-yl)-5-fluoropicolinamide was obtained. LCMS (*m/z*): 455.3 (MH^+); LC R_t = 2.09 min.

Synthesis of 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)-cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide



[0252] Following Method 9, 2-(3-(3-aminopyridin-4-yl)cyclohexyl)iso-indoline-1,3-dione and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide was obtained. LCMS (*m/z*): 523.2/525.2 (MH^+); LC R_t = 3.31 min.

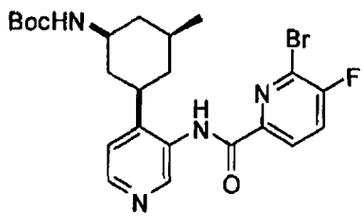
Synthesis of 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide



[0253] Following Method 9, 2-(3-(3-aminopyridin-4-yl)cyclohexyl)-isoindoline-1,3-dione and 3-amino-6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide was obtained. LCMS (*m/z*): 538.1/540.1 (MH^+); LC R_t = 3.46 min.

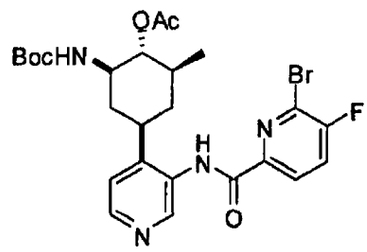
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Synthesis of tert-butyl (1S,3R,5S)-3-(3-(6-bromo-5-fluoropicolinamido)-pyridin-4-yl)-5-methylcyclohexylcarbamate



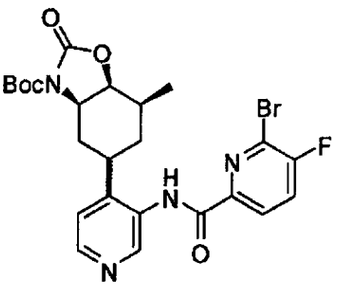
[0254] Following Method 9, tert-butyl (1S,3R,5S)-3-(3-aminopyridin-4-yl)-5-methylcyclohexylcarbamate and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, tert-butyl (1S,3R,5S)-3-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-5-methylcyclohexylcarbamate was obtained. LCMS (*m/z*): 507.1/509.1 (MH^+), R_t = 0.90 min.

Synthesis of (1R,2R,4R,6S)-4-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate



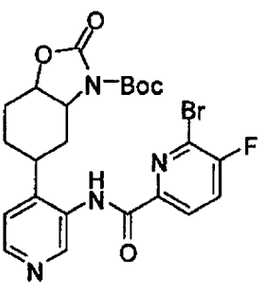
[0255] Following Method 9, (1R,2R,4R,6S)-4-(3-aminopyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, (1R,2R,4R,6S)-4-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate was obtained. LCMS (*m/z*): 567.2 (MH^+), R_t = 0.82 min.

Synthesis of (+/-)-tert-butyl 5-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate



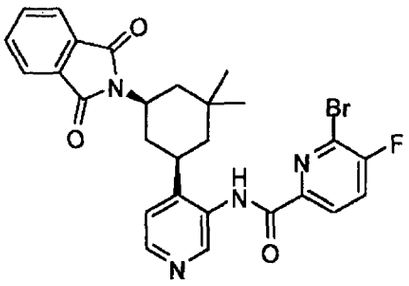
[0256] Following Method 9, (+/-)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, (+/-)-tert-butyl 5-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-7-methyl-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate was obtained. LCMS (*m/z*): 549.2/551.2 (MH^+), R_t = 0.78 min.

Synthesis of tert-butyl 5-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate



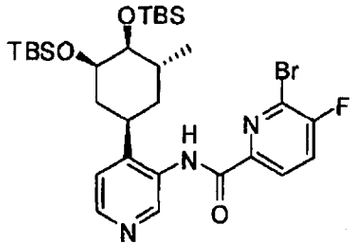
[0257] Following Method 9, tert-butyl 5-(3-aminopyridin-4-yl)-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, tert-butyl 5-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate was obtained. LCMS (*m/z*): 537.1 (MH^+); LCMS R_t = 0.71 min.

Synthesis of 6-bromo-N-(4-((1R,5R)-5-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylcyclohexyl)pyridin-3-yl)-5-fluoropicolinamide



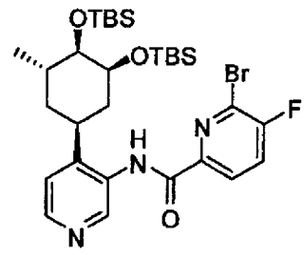
[0258] Following Method 9, 2-((1R,5R)-5-(3-aminopyridin-4-yl)-3,3-dimethylcyclohexyl)isoindoline-1,3-dione and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, 6-bromo-N-(4-((1R,5R)-5-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylcyclohexyl)pyridin-3-yl)-5-fluoropicolinamide was obtained. LCMS (*m/z*): 551/553 (MH^+), R_t = 0.95 min.

Synthesis of N-(4-((1R,3R,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-yl)-6-bromo-5-fluoropicolinamide



[0259] Following Method 9, 4-((1R,3R,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, N-(4-((1R,3R,4S,5R)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-yl)-6-bromo-5-fluoropicolinamide was obtained. LCMS (*m/z*): 652.5, 652.4 (MH^+); LC R_t = 5.82 min.

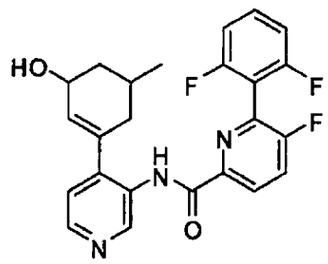
Synthesis of N-(4-((1S,3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-yl)-6-bromo-5-fluoropicolinamide



[0260] Following Method 9, 4-((1S,3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine and 6-bromo-5-fluoropicolinic acid were coupled and following addition of EtOAc and washing with H_2O, $NaCl_{(sat.)}$ and drying over $MgSO_4$, N-(4-((1S,3S,4R,5S)-3,4-bis(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-yl)-6-bromo-5-fluoropicolinamide was obtained. LCMS (*m/z*): 652.5, 652.4 (MH^+); LC R_t = 5.83 min.

Method 10

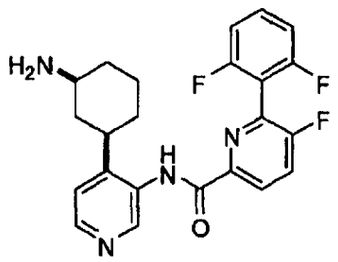
Synthesis of 6-(2,6-difluorophenyl)-5-fluoro-N-(4-(3-hydroxy-5-methylcyclohex-1-enyl)pyridin-3-yl)picolinamide



[0261] A solution of 6-bromo-N-(4-(3-(tert-butyldimethylsilyloxy)-5-methyl-cyclohex-1-enyl)pyridin-3-yl)-5-fluoropicolinamide (1.0 equiv), 2,6-difluorophenyl boronic acid (3.0 equiv.), tetrakistriphenylphosphine (0.2 equiv.) and triethylamine (3.0 equiv.) in 1:1 EtOH/toluene (0.1 M) was heated at 120 °C with microwave irradiation for 1200 seconds. Upon cooling, removal of the volatiles in vacuo, the Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting TBDMS ether was deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, 6-(2,6-difluorophenyl)-5-fluoro-N-(4-(3-hydroxy-

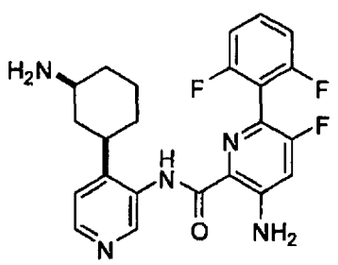
5-methylcyclohex-1-enyl)pyridin-3-yl)picolinamide as the TFA salt.. LCMS (m/z): 438.2 (MH+); LC Rt = 2.00 min.

Synthesis of N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide



[0262] A solution of 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)-cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide (1.0 equiv), 2,6-difluorophenyl boronic acid (3.0 equiv.), tetrakistriphenylphosphine (0.2 equiv.) and triethylamine (3.0 equiv.) in 1:1 EtOH/toluene (0.1 M) was heated at 120 °C with microwave irradiation for 1200 seconds. Upon cooling, removal of the volatiles *in vacuo*, the Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting phthalimide group was deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide as the TFA salt. LCMS (m/z): 427.2 (MH+); LC Rt = 2.26 min.

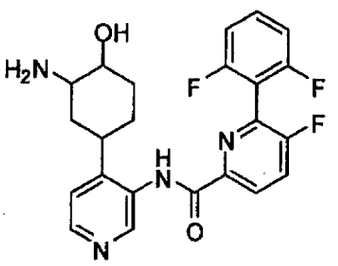
Synthesis of 3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide



[0263] A solution of 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide (1.0 equiv), 2,6-difluorophenyl boronic acid (3.0 equiv.), tetrakistriphenylphosphine (0.2 equiv.) and triethylamine (3.0

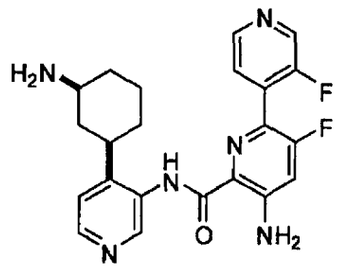
equiv.) in 1:1 EtOH/toluene (0.1 M) was heated at 120 °C with microwave irradiation for 1200 seconds. Upon cooling, removal of the volatiles in vacuo, the Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting phthalimide group was deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, 3-amino-N-(4-((1R,3S)-3-aminocyclo-hexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamideas the TFA salt. LCMS (m/z): 442.2 (MH+); LC Rt = 2.24 min.

Synthesis of N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide



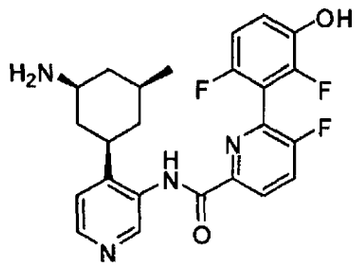
[0264] A solution of tert-butyl 5-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-2-oxohexahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv), 2,6-difluorophenyl boronic acid (3.0 equiv.), tetrakistriphenylphosphine (0.2 equiv.) and triethylamine (3.0 equiv.) in 1:1 EtOH/toluene (0.1 M) was heated at 120 °C with microwave irradiation for 1200 seconds. Upon cooling, removal of the volatiles in vacuo, the Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting cyclic carbamate and Boc groups were deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, N-(4-(3-amino-4-hydroxycyclo-hexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamideas the TFA salt. LCMS (m/z): 443.2 (MH+); LC Rt = 2.11 min.

Synthesis of 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-3,3'-difluoro-2,4'-bipyridine-6-carboxamide



[0265] A solution of 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxoisoindolin-2-yl)cyclohexyl)pyridin-3-yl)-5-fluoropicolinamide (1.0 equiv), 3-fluoropyridin-4-yl-boronic acid (3.0 equiv.), tetrakistriphenylphosphine (0.2 equiv.) and triethylamine (3.0 equiv.) in 1:1 EtOH/toluene (0.1 M) was heated at 120 °C with microwave irradiation for 1200 seconds. Upon cooling, removal of the volatiles in vacuo, the Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting phthalimide group was deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)-pyridin-3-yl)-3,3'-difluoro-2,4'-bipyridine-6-carboxamide as the TFA salt. LCMS (m/z): 425.1 (MH+); LC Rt = 2.08 min.

Synthesis of N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinamide

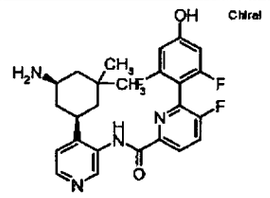
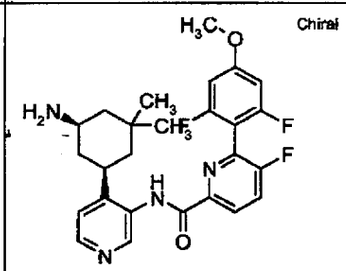
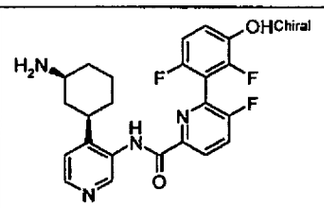
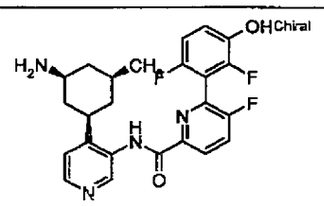


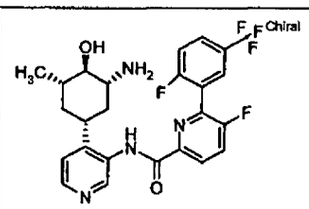
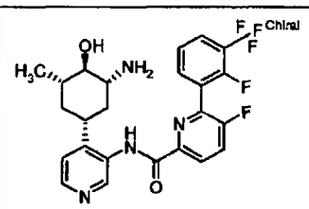
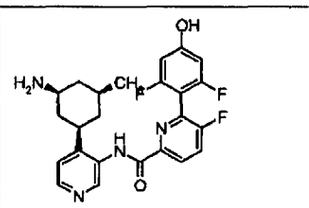
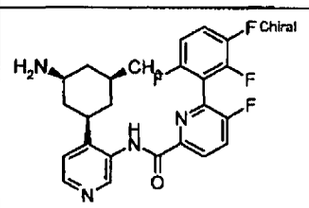
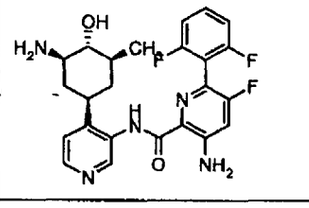
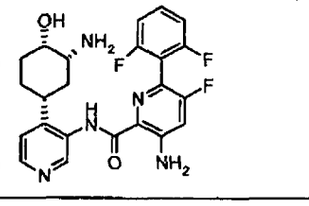
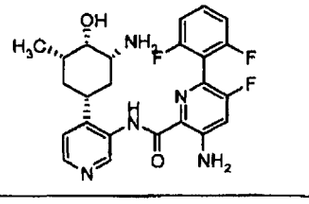
[0266] To a solution of tert-butyl (1S,3R,5S)-3-(3-(6-bromo-5-fluoropicolinamido)pyridin-4-yl)-5-methylcyclohexylcarbamate (1.0 equiv.) in a microwave vial was added 2,6-difluoro-3-hydroxyphenylboronic acid (5.0 equiv.), KF (5.5 equiv.) and $Pd_2(dba)_3$ (0.2 equiv.) followed by THF and water (10:1, 0.03 M). To

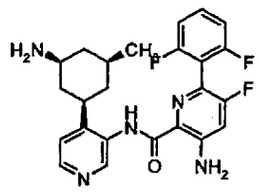
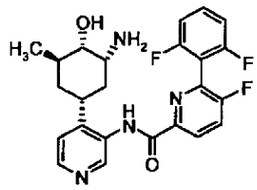
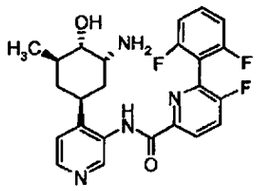
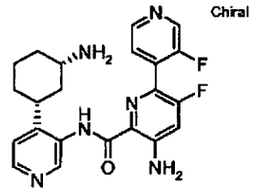
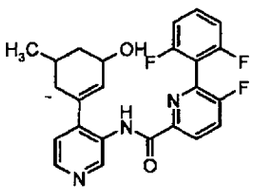
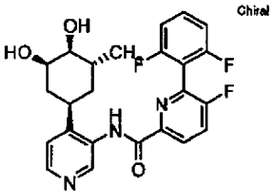
this mixture was added $P(t\text{-}Bu)_3$ (0.4 equiv.) and the reaction was heated in the microwave at 100 °C for 30 min. The organic phase was then separated, the aqueous layer was washed with ethyl acetate, and the organics were combined and concentrated *in vacuo*. The crude mixture was purified via prep-HPLC, the product fractions were lyophilized and the resulting BOC group was deprotected as described in Method 9 yielding, after RP HPLC purification and lyophilization, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinamide as the TFA salt. LCMS (m/z): 457.2 (MH+); LC Rt = 2.17 min.

[0267] The following compounds were prepared using Method 10:

TABLE 2

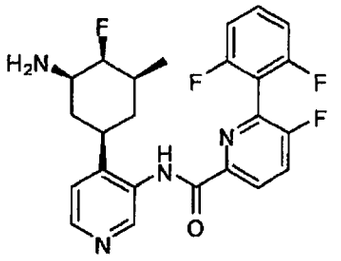
Example No./ NVP ID	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
122		471.2	0.58	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide
123		485.2	0.65	N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide
124		443.2	0.54	N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinamide
125		457.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-3-hydroxyphenyl)-5-fluoropicolinamide

Example No./ NVP ID	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
126		507.1	0.65	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-5-(trifluoromethyl)phenyl)picolinamide
127		507.1	0.65	N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2-fluoro-3-(trifluoromethyl)phenyl)picolinamide
128		457.2	0.58	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide
129		459.2	0.62	N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-5-fluoro-6-(2,3,6-trifluorophenyl)picolinamide
130		472.1	0.56	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
131		458.0	0.57	3-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
132		472.1	0.56	3-amino-N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

Example No./ NVP ID	Structure	LC/MS (M+H on UPCL)	LC/MS (Rf on UPCL)	Chemical Name
133		456.3	0.60	3-amino-N-(4-(3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
134		457.1	0.57	N-(4-(-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
135		457.1	0.55	N-(4-(3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
136		425.1	0.46	5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-3,3'-difluoro-2,4'-bipyridine-6-carboxamide
137		440.2	0.75	6-(2,6-difluorophenyl)-5-fluoro-N-(4-(3-hydroxy-5-methylcyclohex-1-enyl)pyridin-3-yl)picolinamide
138		458.2	0.64	6-(2,6-difluorophenyl)-N-(4-((1R,3R,4S,5R)-3,4-dihydroxy-5-methylcyclohexyl)pyridin-3-yl)-5-fluoropicolinamide

Example 139

Synthesis of N-(4-((1R,3R,4S,5S)-3-amino-4-fluoro-5-methylcyclohexyl)-pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide



[0268] To a solution of tert-butyl (1R,2R,3S,5R)-5-(3-(6-(2,6-difluorophenyl)-5-fluoropicolinamido)pyridin-4-yl)-2-hydroxy-3-methylcyclohexylcarbamate (1.0 equiv.) in DCM (0.04 M) at 0 °C was added DAST (1.0 equiv.). The reaction was stirred for 1.5 h at 0 °C, then TFA (10 equiv.) was added to the reaction. After 2 h, the reaction was concentrated *in vacuo* and the residue was purified via prep-HPLC to afford N-(4-((1R,3R,4S,5S)-3-amino-4-fluoro-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluoro-phenyl)-5-fluoropicolinamide as the TFA salt. LCMS (m/z): 459.3 (MH+); LC Rt = 2.39 min.

[0269] In addition to LC/MS and LC characterization, representative compounds were analyzed by ^{1}H-NMR. The following are typical spectra of the compounds of the invention.

Example #	^{1}H-NMR data
50	HCl salt, 1H-NMR (400 MHz, DMSO-d6): d 10.54 (bs, 1H), 8.80 (bs, 1H), 8.55 (d, 1H), 8.34 (dd, 1H), 8.20 (t, 1H), 8.00 (bs, 2H), 7.69 (m, 1H), 7.56 (d, 1H), 7.34 (t, 2H), 3.10-3.0 (m, 2H), 2.83 (m, 1H), 2.03 (d, 1H), 1.76-1.59 (m, 2H), 1.40 (m, 1H), 1.31-1.21 (m, 1H), 0.92 (d, 3H).
52	HCl salt, 1H-NMR (DMSO-d6): d 10.4 (s, 1H), 8.71 (s, 1H), 8.37 (d, 1H), 8.14-8.20 (m, 2H), 7.94 (bs, 2H), 7.86-7.88 (m, 2H), 7.54-7.58 (m, 1H), 7.30 (d, 1H), 7.22-7.26 (m, 2H), 2.09-3.02 (m, 2H), 2.78 (m, 1H), 1.96-1.99 (m, 1H), 1.68-1.71 (m, 1H), 1.60 (q, 1H), 1.37 (m, 1H), 1.15-1.24 (m, 1H), 0.88 (d, 3H)
70	HCl salt, 1H NMR (400 MHz, DMSO-d6): d 10.59 (s, 1H), 8.92 (s, 1H), 8.62 (d, 1H), 8.37 (dd, 1H), 8.23 (t, 1H), 8.19 (bs, 2H), 7.68-7.71 (m, 2H), 7.36-7.40 (m, 2H),3.01-3.10 (m, 2H), 2.01-2.05 (m, 1H), 1.94-1.97 (m, 1H), 1.72-1.76 (m, 1H), 1.46-1.53 (m, 2H), 1.01-1.13 (m, 2H), 0.89 (d, 3H)

85	HCl salt, 1H NMR (DMSO-d6): d 10.37 (s, 1H), 8.61 (s, 1H), 8.41 (d, 1H), 8.29 (dd, 1H), 8.13 (t, 1H), 7.8 (bs, 2H), 7.69-7.61 (m, 1H), 7.34-7.28 (m, 3H), 3.061 (m, 1H), 2.86 (m, 1H), 1.76-1.63 (m, 2H), 1.53-1.47 (m, 1H), 1.4-1.34 (m, 2H), 0.82 (d, 3H).
88	HCl salt, 1H NMR (DMSO-d6): d 10.42 (s, 1H), 8.62 (s, 1H), 8.46 (m, 1H), 8.32 (m, 1H), 8.18 (t, 1H), 7.76 (m, 2H), 7.67 (m, 1H), 7.35 (m, 3H), 5.33 (brs, 1H), 3.108 (m, 2H), 2.88 (m, 2H), 1.65 (m, 2H), 1.48 (m, 3H).
96	HCl salt, 1H NMR (400 MHz, CD3OD): d 9.09 (s, 1 H), 8.46 (dd, 1 H), 8.39 (dd, 1 H), 8.05 (t, 1 H), 7.57 - 7.67 (m, 1 H), 7.53 (d, 1 H), 7.16 - 7.25 (m, 2 H), 4.03 - 4.12 (m, 1 H), 3.85 - 3.94 (m, 1 H), 3.20 (s, 3 H), 2.70 - 2.80 (m, 1 H), 1.67 - 1.79 (m, 1 H), 0.83 (d, 3 H).
99	free-base, 1H NMR (CDCl3): d 9.93(s, 1H), 9.38(s, 1H), 8.40-8.45(m,1H), 8.40(d, 1H), 7.74-7.80(m, 1H), 7.47-7.55(m, 1H), 7.19(d, 1H), 7.06-7.13(m, 2H), 2.68-2.83(m, 2H), 1.97-2.05(m, 1H), 1.65-1.95(m, 5H), 1.22-1.40(m, 3H), 1.04-1.15(m, 1H).
100	HCl salt, 1H NMR (DMSO-d6): d 10.13(s, 1H), 8.82(s, 1H), 8.41(d, 1H), 7.94(bs, 2H), 7.52-7.62(m, 1H), 7.36(d, 1H), 7.36 (bs, 2H), 7.20-7.31(m, 3H), 2.78-2.88(m, 2H), 1.70-2.02(m, 4H), 1.16-1.54(m, 4H).
102	HCl salt, 1H NMR (400 MHz, DMSO-d6): d 10.59 (s, 1H), 9.30 (s, 1H), 8.54 (d, 1H) 8.08 (br s, 3H), 7.75 (d, 1H), 7.65 (d, 1H), 7.60–7.56 (m, 1H), 7.49 (d, 1H), 7.33 (t, 2H), 4.04 (br s, 1H), 3.16(br s, 2H) 3.05 (br t, 1H), 1.98–1.20 (m, 7H)
116	HCl salt, 1H-NMR (400, d6-DMSO): d 10.47 (s, 1H), 8.56 (s, 1H), 8.33 (dd, 1H), 8.26 (dd, 1H), 8.20 (t, 1H), 7.62-7.72 (m, 1H), 7.30-7.35 (m, 3H), 3.82-3.92 (m, 2H), 3.18-3.22 (m, 1H), 2.84-2.91 (m, 1H), 2.69 (t, J=13.2, 1H), 1.38-1.46 (m, 1H), 0.69 (d, 3H).
128	HCl salt, 1H-NMR (400, d6-DMSO): d 11.00 (s, 1H), 10.46 (s, 1H), 8.55 (d, 1H), 8.29 (dd, 1H), 8.15 (t, 1H), 8.05 (bs, 2H), 7.54 (d, 1H), 6.72 (d, 2H), 3.04 - 3.10 (m, 1H), 2.92-3.04 (m, 1H), 2.01 (d, 1H), 1.95 (d, 1H), 1.74 (d, 1H), 1.42-1.52 (m, 2H), 0.97-1.08 (m, 2 H), 0.88 (d, 3H).

Example 140

Pim1 ATP depletion assay

[0270] The activity of PIM1 is measured using a luciferase-luciferin based ATP detection reagent to quantify ATP depletion resulting from kinase-catalyzed phosphoryl transfer to a peptide substrate. Compounds to be tested are dissolved in 100% DMSO and directly distributed into white 384-well plates at 0.5 µl per well. To start the reaction, 10 µl of 5 nM Pim1 kinase and 80 µM BAD peptide (RSRHSSYPAGT-OH) in assay buffer (50 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 0.05% BSA) is added into each well. After 15 minutes, 10 µl of 40 µM ATP in assay buffer is added. Final assay concentrations are 2.5 nM PIM1, 20 µM ATP, 40 µM BAD peptide and 2.5% DMSO. The reaction is performed until approximately 50% of the ATP is depleted, then stopped with the addition of 20 µl KinaseGlo Plus (Promega

Corporation) solution. The stopped reaction is incubated for 10 minutes and the remaining ATP detected via luminescence on the Victor2 (Perkin Elmer). Compounds of the foregoing examples were tested by the Pim1 ATP depletion assay and found to exhibit an IC_{50} values as shown in Table 3, below. IC_{50}, the half maximal inhibitory concentration, represents the concentration of a test compound that is required for 50% inhibition of its target *in vitro*.

Example 141

Pim2 ATP depletion assay

[0271] The activity of PIM2 is measured using a luciferase-luciferin based ATP detection reagent to quantify ATP depletion resulting from kinase-catalyzed phosphoryl transfer to a peptide substrate. Compounds to be tested are dissolved in 100% DMSO and directly distributed into white 384-well plates at 0.5 µl per well. To start the reaction, 10 µl of 10 nM Pim2 kinase and 20 µM BAD peptide (RSRHSSYPAGT-OH) in assay buffer (50 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 0.05% BSA) is added into each well. After 15 minutes, 10 µl of 8 µM ATP in assay buffer is added. Final assay concentrations are 5 nM PIM2, 4 µM ATP, 10 µM BAD peptide and 2.5% DMSO. The reaction is performed until approximately 50% of the ATP is depleted, then stopped with the addition of 20 µl KinaseGlo Plus (Promega Corporation) solution. The stopped reaction is incubated for 10 minutes and the remaining ATP detected via luminescence on the Victor2 (Perkin Elmer). Compounds of the foregoing examples were tested by the Pim2 ATP depletion assay and found to exhibit an IC_{50} values as shown in Table 3, below.

Example 142

Pim3 ATP depletion assay

[0272] The activity of PIM3 is measured using a luciferase-luciferin based ATP detection reagent to quantify ATP depletion resulting from kinase-catalyzed phosphoryl transfer to a peptide substrate. Compounds to be tested are dissolved in 100% DMSO and directly distributed into white 384-well plates at 0.5 µl per well. To start the reaction, 10 µl of 10 nM Pim3 kinase and 200 µM BAD peptide (RSRHSSYPAGT-OH) in assay buffer (50 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM

DTT, 0.05% BSA) is added into each well. After 15 minutes, 10 µl of 80 µM ATP in assay buffer is added. Final assay concentrations are 5 nM PIM1, 40 µM ATP, 100 µM BAD peptide and 2.5% DMSO. The reaction is performed until approximately 50% of the ATP is depleted, then stopped by the addition of 20 µl KinaseGlo Plus (Promega Corporation) solution. The stopped reaction is incubated for 10 minutes and the remaining ATP detected via luminescence on the Victor2 (Perkin Elmer). Compounds of the foregoing examples were tested by the Pim3 ATP depletion assay and found to exhibit an IC_{50} values as shown in Table 3, below.

Example 143

Cell Proliferation Assay

[0273] KMS11 (human myeloma cell line), were cultured in IMDM supplemented with 10% FBS, sodium pyruvate and antibiotics. Cells were plated in the same medium at a density of 2000 cells per well into 96 well tissue culture plates, with outside wells vacant, on the day of assay. MM1.s (human myeloma cell line), were cultured in RPMI1640 supplemented with 10% FBS, sodium pyruvate and antibiotics. Cells were plated in the same medium at a density of 5000 cells per well into 96 well tissue culture plates, with outside wells vacant, on the day of assay.

[0274] Test compounds supplied in DMSO were diluted into DMSO at 500 times the desired final concentrations before dilution into culture media to 2 times final concentrations. Equal volumes of 2x compounds were added to the cells in 96 well plates and incubated at 37 °C for 3 days.

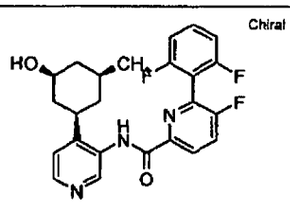
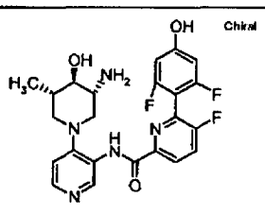
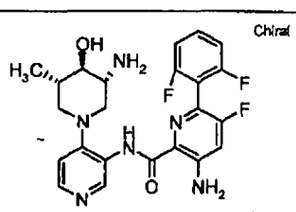
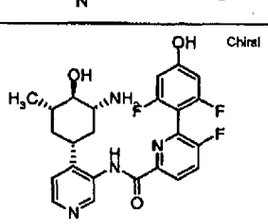
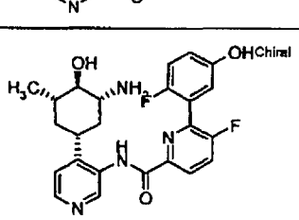
[0275] After 3 days plates were equilibrated to room temperature and equal volume of CellTiter-Glow Reagent (Promega) was added to the culture wells. The plates were agitated briefly and luminescent signal was measured with luminometer. The percent inhibition of the signal seen in cells treated with DMSO alone vs. cells treated with control compound was calculated and used to determine EC_{50} values (i.e., the concentration of a test compound that is required to obtain 50% of the maximum effect in the cells) for tested compounds, as shown in Table 3.

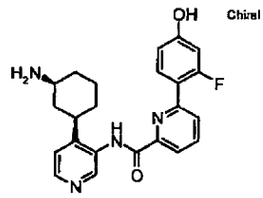
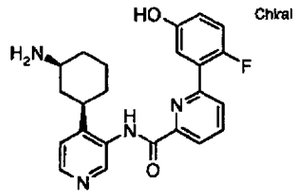
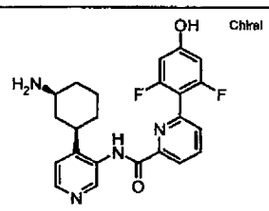
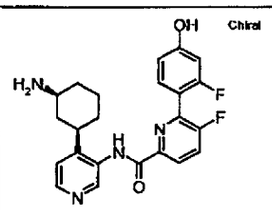
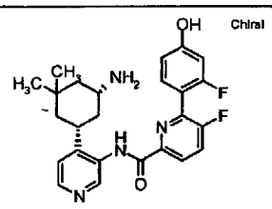
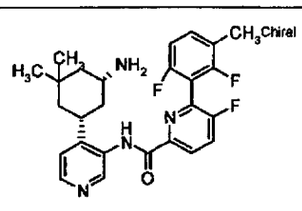
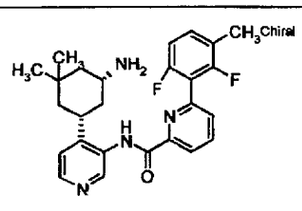
[0276] Using the procedures of Examples 140 (Pim1 ATP depletion assay), 141 (Pim2 ATP depletion assay), and 142 (Pim3 ATP depletion assay), the IC_{50}

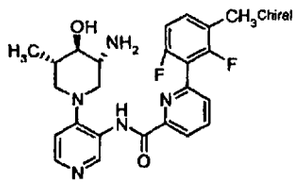
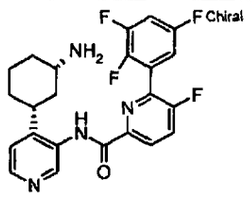
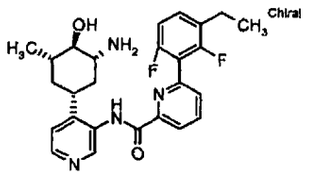
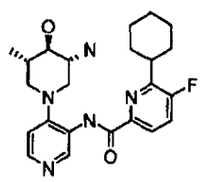
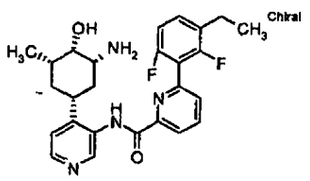
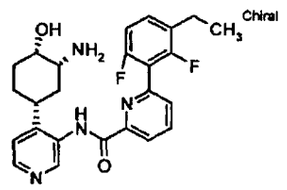
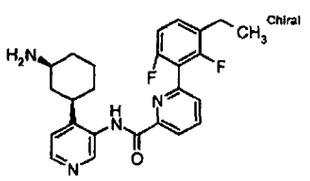
concentration of compounds of the previous examples were determined as shown in the following table 3.

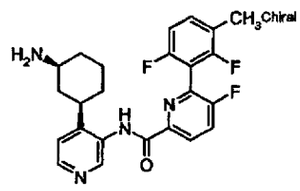
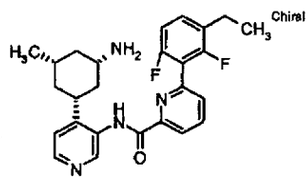
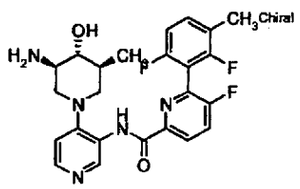
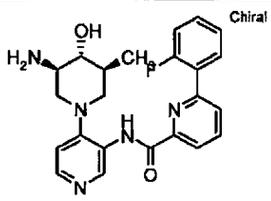
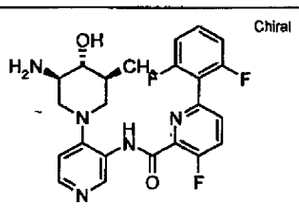
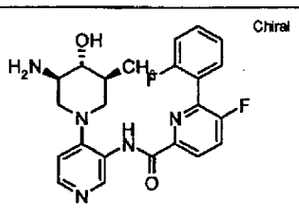
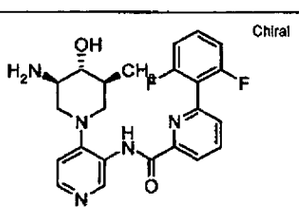
[0277] Using the procedures of Example 143 (cell proliferation assay), the EC_{50} concentration of compounds of the examples in were determined in KMS11 cells as shown in Table 3.

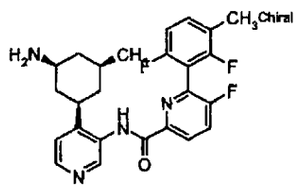
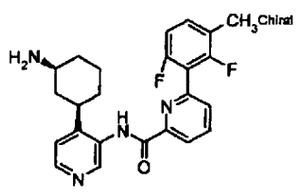
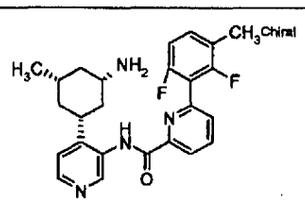
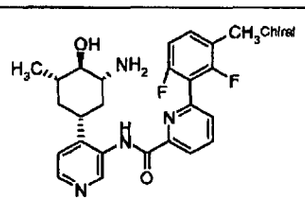
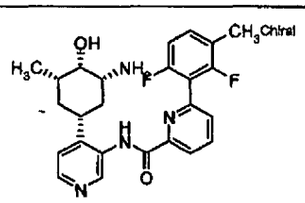
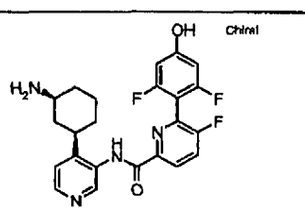
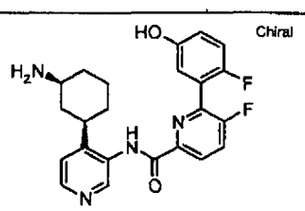
TABLE 3

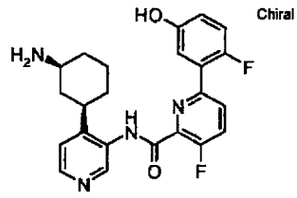
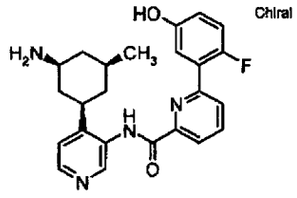
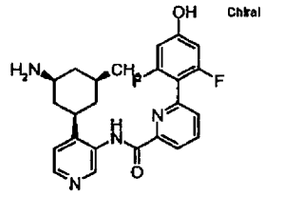
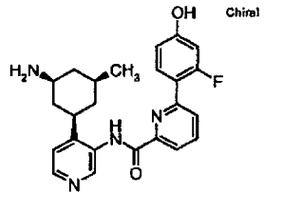
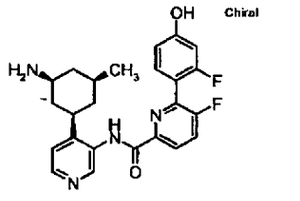
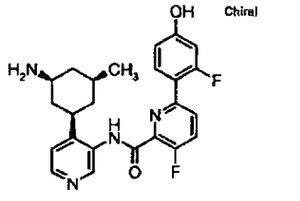
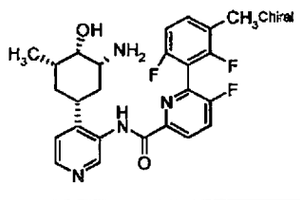
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
1		0.001	0.018	0.006	7.6
2		0.001	0.001	0.001	0.07
3		0.001	0.001	0.001	0.01
4		0.001	0.003	0.002	1.3
5		0.003	0.020	0.009	4.8

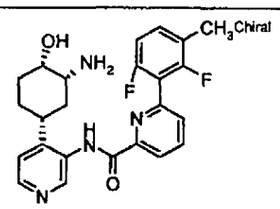
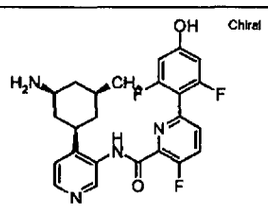
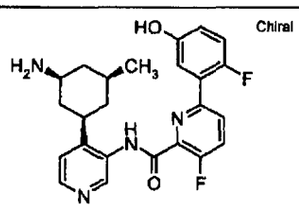
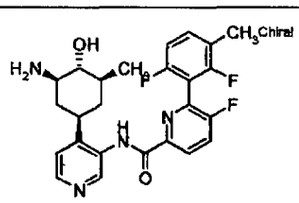
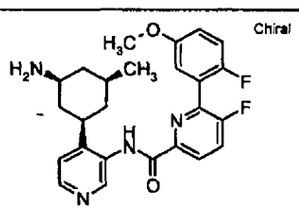
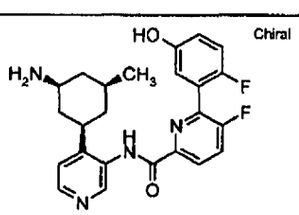
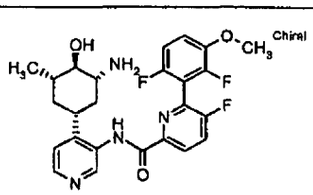
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
6		0.002	0.012	0.003	4.1
7		0.001	0.008	0.002	0.33
8		0.001	0.004	0.002	0.51
9		0.001	0.008	0.002	1.6
10		0.001	0.012	0.006	2.9
11		0.001	0.005	0.004	2.6
12		0.001	0.010	0.004	2.4

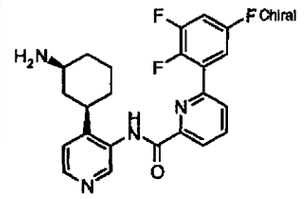
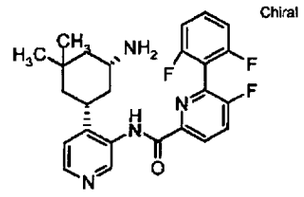
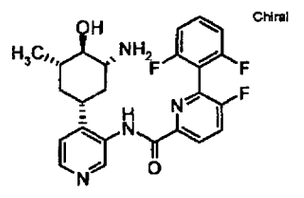
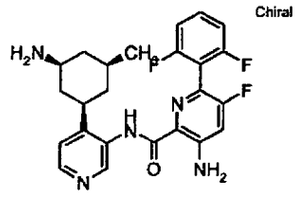
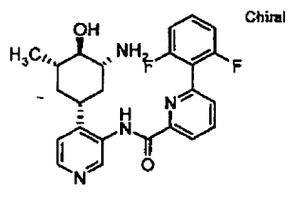
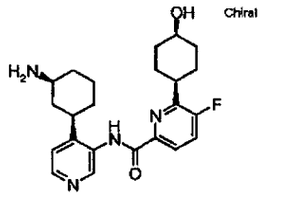
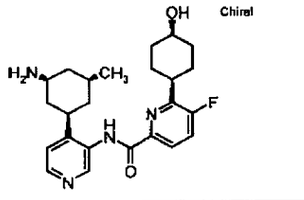
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
13		0.001	0.004	0.003	0.67
14		0.006	0.040	0.012	8.5
15		0.003	0.027	0.006	5.5
16		0.001	0.003	0.003	1.7
17		0.001	0.013	0.005	3.5
18		0.003	0.062	0.007	6.3
19		0.003	0.054	0.007	4.5

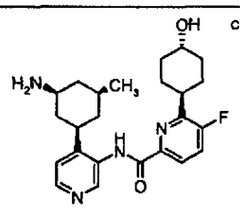
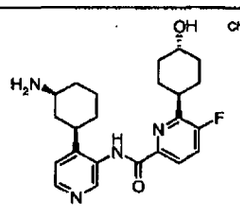
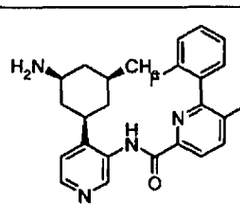
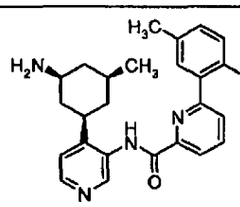
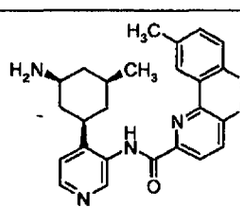
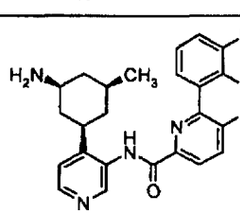
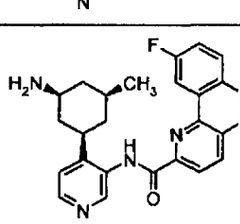
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
20		0.001	0.007	0.003	1.5
21		0.002	0.013	0.006	3.3
22		0.001	0.002	0.003	0.21
23		0.002	0.005	0.003	1.9
24		0.001	0.002	0.001	0.62
25		0.001	0.002	0.002	0.37
26		0.001	0.002	0.002	0.29

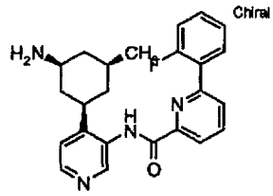
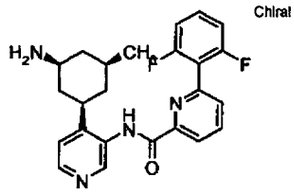
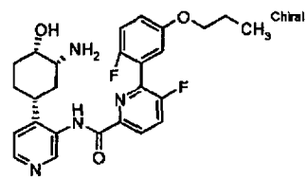
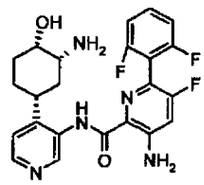
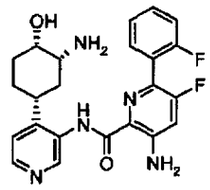
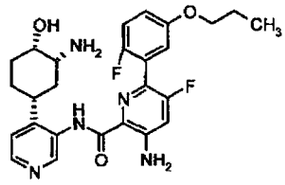
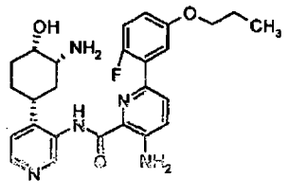
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
27		0.001	0.003	0.002	0.95
28		0.001	0.011	0.002	2.2
29		0.001	0.004	0.003	1.4
30		0.002	0.012	0.004	2.1
31		0.002	0.007	0.004	1.1
32		0.001	0.004	0.003	0.39
33		0.001	0.009	0.003	1.4

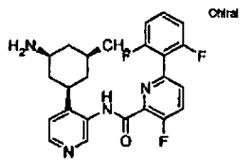
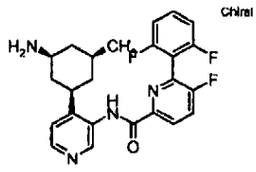
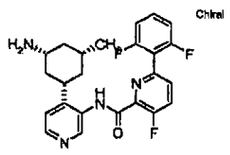
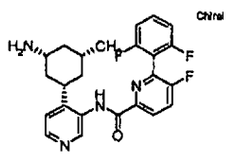
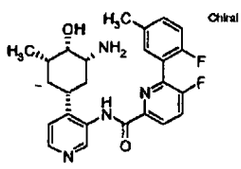
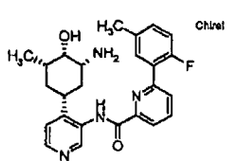
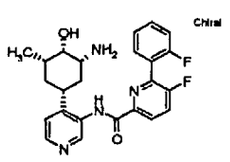
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
34		0.004	0.067	0.006	6.0
35		0.001	0.006	0.003	0.67
36		0.001	0.003	0.003	0.24
37		0.002	0.007	0.005	1.5
38		0.001	0.004	0.003	0.73
39		0.007	0.028	0.012	6.6
40		0.001	0.003	0.002	0.99

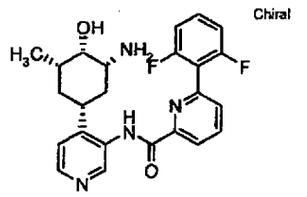
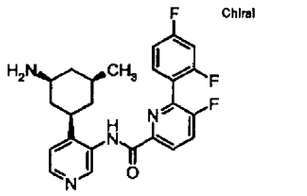
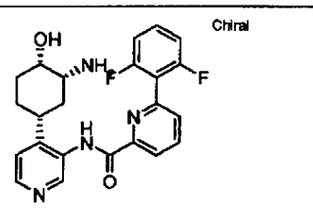
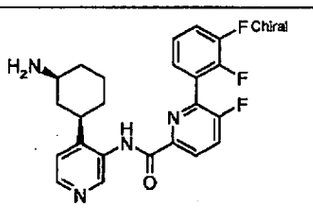
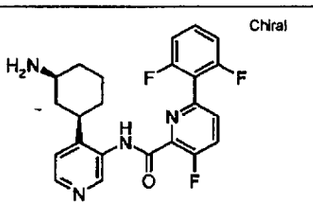
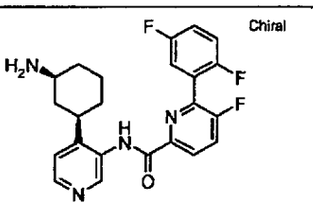
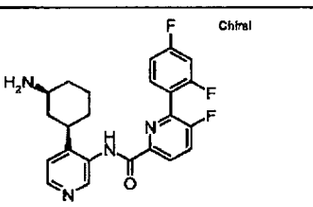
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
41		0.002	0.027	0.005	2.0
42		0.001	0.002	0.002	3.0
43		0.001	0.006	0.002	2.2
44		0.001	0.002	0.002	1.9
45		0.001	0.002	0.002	1.3
46		0.001	0.002	0.002	0.76
47		0.001	0.004	0.003	1.3

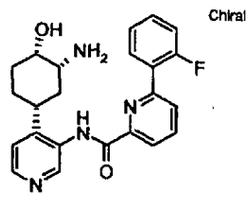
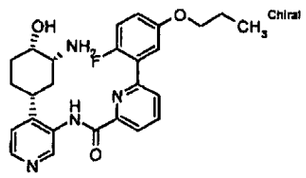
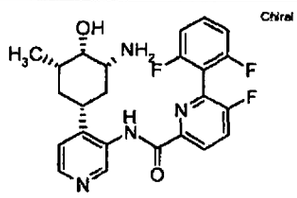
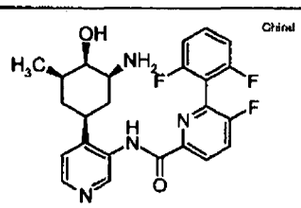
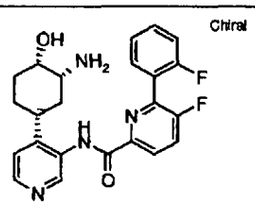
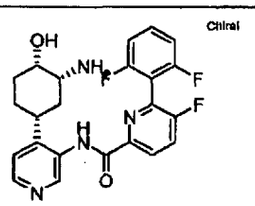
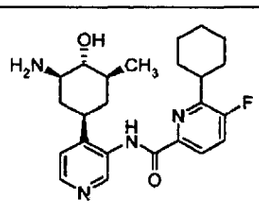
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
48		0.007	0.076	0.009	
49		0.001	0.003	0.002	1.8
50		0.001	0.003	0.002	1.2
51		0.001	0.002	0.001	0.31
52		0.001	0.003	0.002	0.83
53		0.010	0.149	0.065	>10
54		0.003	0.026	0.024	3.8

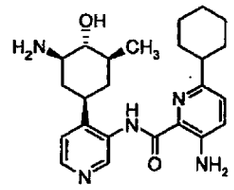
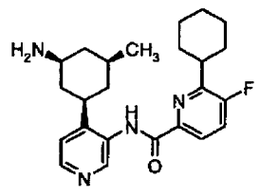
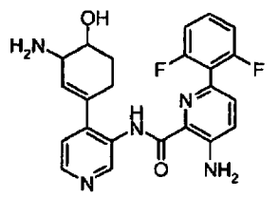
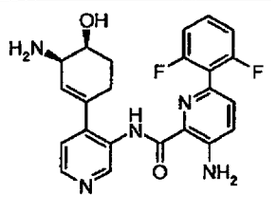
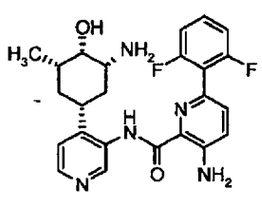
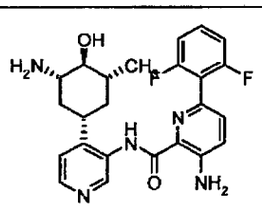
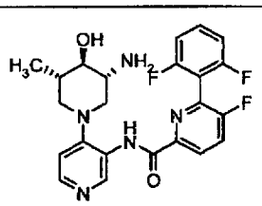
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
55		0.003	0.011	0.030	4.9
56		0.011	0.081	0.102	>10
57		0.001	0.004	0.002	1.4
58		0.001	0.008	0.003	1.8
59		0.001	0.003	0.002	1.1
60		0.001	0.005	0.003	1.3
61		0.001	0.006	0.004	1.2

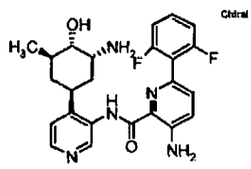
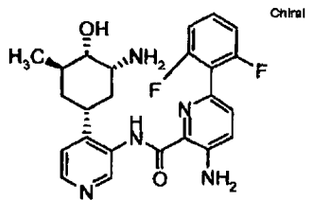
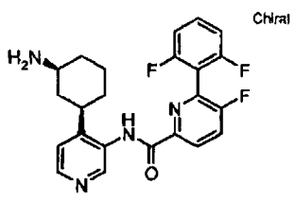
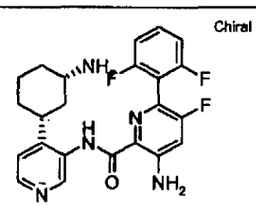
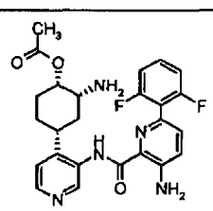
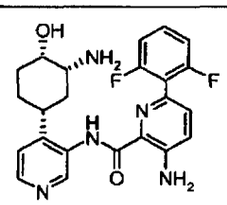
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
62		0.001	0.007	0.003	2.4
63		0.001	0.003	0.002	0.53
64		0.002	0.076	0.005	5.6
65		0.001	0.004	0.003	0.16
66		0.001	0.004	0.002	0.52
67		0.001	0.007	0.003	1.2
68		0.001	0.008	0.004	1.4

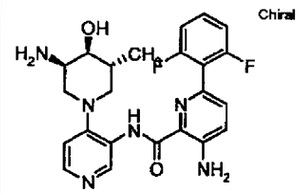
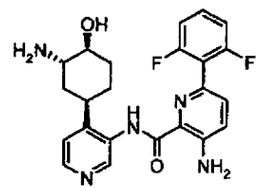
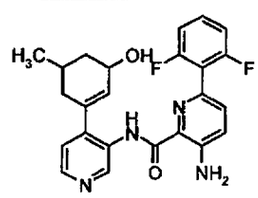
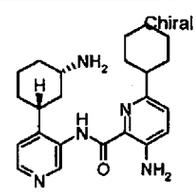
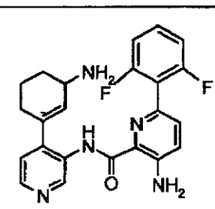
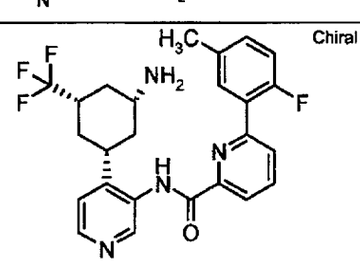
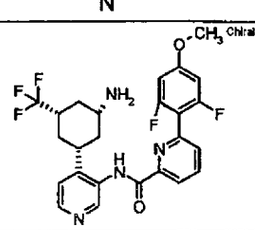
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
69		0.003	0.007	0.006	1.0
70		0.001	0.002	0.002	0.48
71		0.662	1.947	1.05	
72		0.095	0.522	0.369	
73		0.001	0.008	0.004	1.4
74		0.001	0.017	0.004	2.9
75		0.001	0.008	0.003	2.1

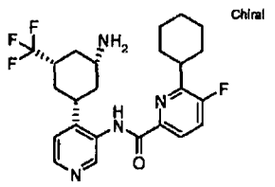
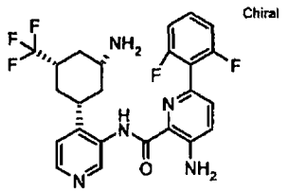
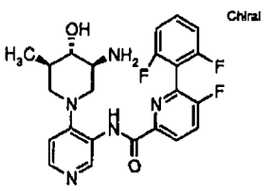
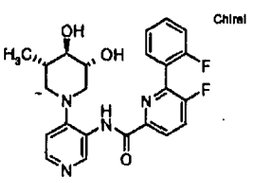
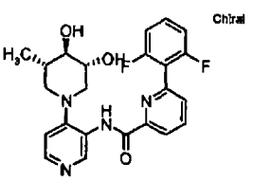
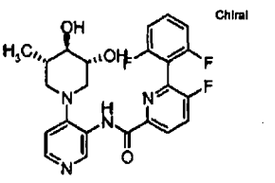
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
76		0.001	0.003	0.002	0.83
77		0.001	0.013	0.003	3.9
78		0.002	0.015	0.003	3.6
79		0.002	0.020	0.003	4.6
80		0.006	0.044	0.007	7.9
81		0.002	0.025	0.005	5.940
82		0.003	0.080	0.009	>10

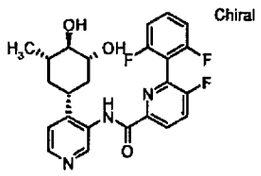
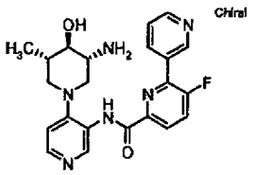
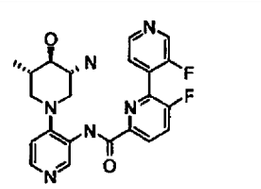
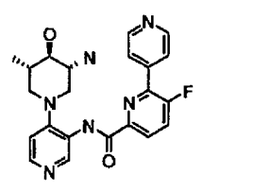
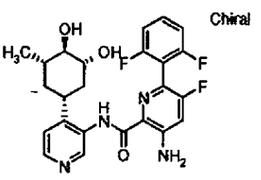
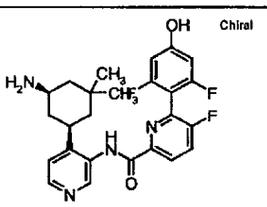
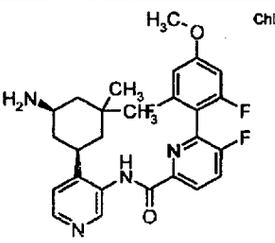
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
83		0.004	0.048	0.005	>10
84		0.004	0.163	0.007	6.9
85		0.001	0.003	0.002	0.41
86		0.031	0.124	0.106	6.1
87		0.002	0.035	0.005	7.7
88		0.001	0.011	0.005	0.79
89		0.008	0.021	0.029	

Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
90		0.003	0.010	0.012	
91		0.003	0.012	0.021	2.9
92		0.002	0.009	0.005	
93		0.001	0.008	0.005	
94		0.001	0.003	0.005	0.239
95		0.001	0.005	0.006	0.537
96		0.001	0.001	0.001	0.03

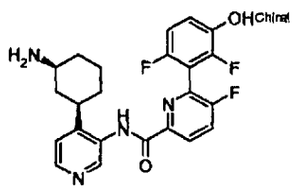
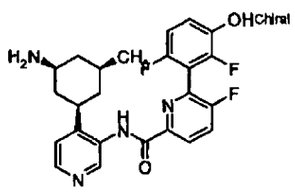
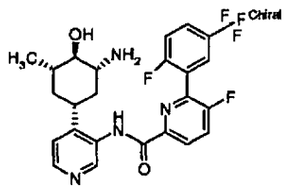
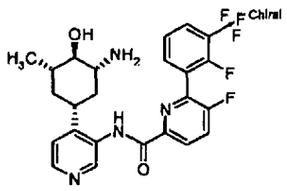
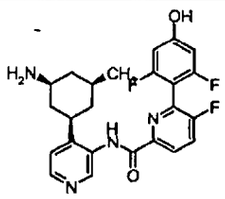
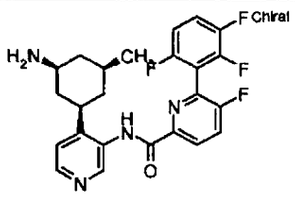
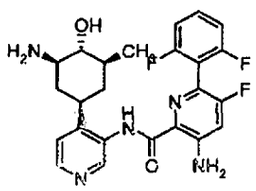
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
97		0.002	0.010	0.007	3.3
98		0.002	0.005	0.005	0.81
99		0.001	0.005	0.003	0.93
100		0.001	0.001	0.001	0.28
101		0.002	0.007	0.005	
102		0.001	0.004	0.004	0.87

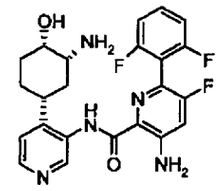
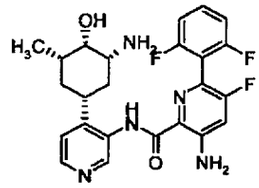
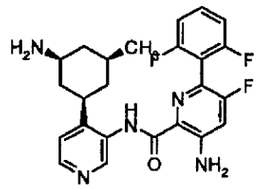
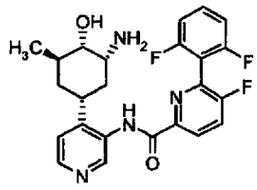
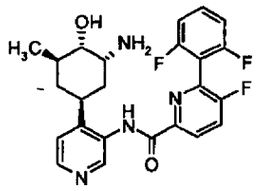
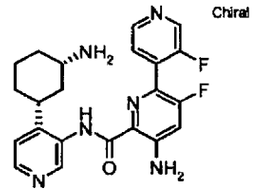
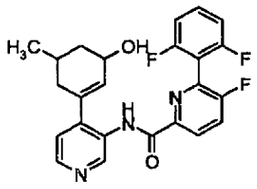
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
103		0.002	0.008	0.004	
104		0.003	0.013	0.005	
105		0.001	0.006	0.004	
106		0.005	0.022	0.014	
107		0.002	0.007	0.006	0.93
108		0.001	0.007	0.003	
109		0.001	0.002	0.002	

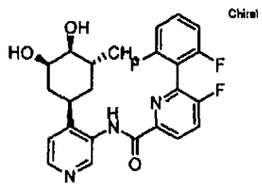
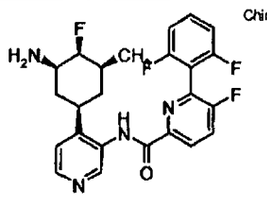
Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
110		0.001	0.001	0.001	
111		0.002	0.005	0.011	
112		0.001	0.001	0.001	
113		0.004	0.089	0.028	
114		0.001	0.003	0.001	0.64
115		0.001	0.002	0.001	0.59
116		0.001	0.001	0.001	0.29

Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
117	 Chiral	0.001	0.006	0.002	2.5
118	 Chiral	0.004	0.029	0.009	4.6
119		0.001	0.004	0.002	1.2
120		0.003	0.018	0.007	8.5
121	 Chiral	0.001	0.001	0.002	
122	 Chiral	0.001	0.002	0.002	0.23
123	 Chiral	0.001	0.004	0.002	0.49

98

Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
124		0.001	0.002	0.001	0.78
125		0.001	0.001	0.001	0.41
126		0.002	0.068	0.017	
127		0.011	0.131	0.027	
128		0.001	0.001	0.001	0.26
129		0.001	0.003	0.002	1.2
130		0.002	0.007	0.008	1.0

Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
131		0.002	0.007	0.006	0.43
132		0.001	0.005	0.006	0.38
133		0.001	0.004	0.007	0.24
134		0.002	0.016	0.008	1.9
135		0.023	0.088	0.036	
136		0.002	0.024	0.009	6.4
137		0.001	0.020	0.007	

Example No./ NVP ID	Structure	Pim1 IC50 µM	Pim2 IC50 µM	Pim3 IC50 µM	KMS11-luc EC50 µM
138		0.002	0.045	0.006	
139		0.001	0.005	0.004	1.9

Example 144

Biological Method: Pharmacology Target Modulation and Efficacy Study in Multiple Myeloma Xenograft Model

[0278] KMS11-luc multiple myeloma cancer cells, obtained from Suzanne Trudel (University Health Network, Toronto, Canada), express stable luciferase achieved by retroviral transfection and were maintained in DMEM supplemented with 10% heat-inactivated fetal bovine serum with 1% glutamine (Invitrogen, Inc.). Female SCID/bg mice (8-12 weeks old, 20-25g, Charles River) were used for all *in vivo* pharmacology studies. The mice were housed and maintained in accordance with state and federal guidelines for the humane treatment and care of laboratory animals, and received food and water *ad libitum.* Cancer cells were harvested from mid-log phase cultures, viable cell count was established with an automated cell counter (Vi-CELL, Beckman-Coulter), and cells were resuspended in equal parts HBSS and Matrigel (Invitrogen, Inc.). Ten millions cells were subcutaneously injected into the right flank of each mouse. Compound treatment was initiated when tumor size reached 250-350mm^3 for PK/PD studies, and 150-250mm^3 for efficacy studies, with tumor volumes determined using StudyDirector software (StudyLog Systems, Inc.). All compound treatment was administered orally.

[0279] For *in vivo* target modulation in PK/PD time-course studies, tumor-bearing mice were administered a single oral dose of vehicle or compound at different concentrations. At 1, 8 and 24 hours after dosing, tumor tissues and blood samples were

taken from individual mice. Resected tumor tissues were snap frozen and pulverized using a liquid nitrogen-cooled cryomortar and pestle. Blood samples were taken by cardiac puncture, and plasma was separated utilizing centrifugation tubes containing lithium heparin and plasma separator (BD Microtainer). Frozen tumor samples were lysed in cold buffer (Meso Scale Discovery) supplemented with EDTA free protease inhibitor (Roche), phosphatase inhibitors 1 and 2, and 1M NaF (Sigma) according to manufacturer's instructions. Following homogenization with a dounce apparatus or by MagNA Lyser (Roche), clear supernatant was obtained following centrifugation at 300xg for 30 minutes at 4°C and protein concentration was determined by BCA (BioRad). Target modulation was determined using the Meso Scale phospho-Bad^{Ser112}/total Bad duplex kit, according to manufacturer's instructions. Briefly, an equal amount of protein was loaded into each well of a Meso Scale phospho-Serine^{112}/total Bad duplex 96-well plate (Meso Scale Discovery) and samples were incubated for 30 minutes at room temperature or overnight at 4°C, shaking. Plates were washed with 1x MSD wash buffer, and Sulfo-Tag detection antibody was added to the wells and incubated for 1 hour at room temperature, shaking. The plates were washed again and captured analyte detected following the addition of Read Buffer T to the wells. Plates were read on a SECTOR Imager 6000 Instrument (Meso Scale Discovery). Ratios of the signal from pBad to total Bad were used to correct for variability between samples. Data shown in the following table express the percent inhibition of pBad^{Ser112} phosphorylation relative to total Bad phosphorylation by representative compounds of the invention, normalized to vehicle control group. The extent of modulation is expressed as a percent, relative to vehicle control (*n.d.*, not determined).

Compound of Example No.	1hr	8hr	24hr
99 (50 mg/kg)	40	55	0
99 (100 mg/kg)	62	66	24
70 (25 mg/kg)	34	50	*n.d.*
70 (50 mg/kg)	28	62	0
70 (100 mg/kg)	5	67	68
96 (25 mg/kg)	0	24	*n.d.*
96 (50 mg/kg)	44	69	16
96(100 mg/kg)	58	71	53

[0280] For efficacy studies, tumor-bearing mice were randomized into groups with equivalent tumor volume variation ranging from 150-250mm^3 utilizing the StudyDirector software (StudyLog Systems, Inc.). Following randomization, mice were dosed orally daily or twice daily at multiple compound concentrations in 200µl incipient. Tumor growth and animal body weight was measured at least twice weekly, and daily clinical observations were used to monitor potential toxicities related to the treatment. Animals were removed from study if tumor volume exceeded 2500mm^3, or if body weight loss exceeded 20% of initial measurements.

[0281] Efficacy of the compound of Example 99 was evaluated in the KMS11-luc xenograft model, with mice receiving oral administration of the compound of Example 99 twice daily at 50 and 100 mg/kg, and once daily at 100 mg/kg for 14 days. Dosing was initiated when tumor sizes reached approximately 250mm^3. As shown in Figure 1, the compound of Example 99 exhibited dose-dependant effects *in vivo*, with tumor growth inhibition observed with 50 mg/kg twice daily (92%) and 100 mg/kg twice daily (4% regression). Once daily administration of 100 mg/kg was less efficacious (65%) than when dosed twice daily. These results correlate with the extent and magnitude of pBad^{Ser112} modulation, and suggest that extensive and prolonged target modulation is required for maximum efficacy.

[0282] Efficacy of the compound of Example 70 was evaluated in the KMS11-luc xenograft model, with mice receiving oral administration of the compound of Example 80 twice daily at 25 and 50 mg/kg, and once daily at 100 mg/kg for 14 days. Dosing was initiated when tumor sizes reached approximately 225mm^3. As shown in Figure 2, the compound of Example 70 exhibited dose-dependant effects *in vivo*, with

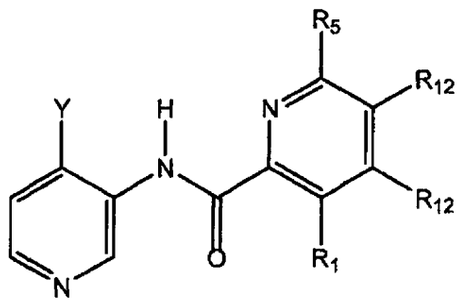
tumor growth inhibition observed for 25 mg/kg (65%) and 50 mg/kg (100%). Significant tumor growth inhibition was also observed for 100 mg/kg once daily (84%).

[0283] Efficacy of the compound of Example 96 was evaluated in the KMS11-luc xenograft model, with mice receiving oral administration of the compound of Example 96 twice daily at 25 and 50 mg/kg, and once daily at 100 mg/kg for 14 days. Dosing was initiated when tumor sizes reached approximately 225mm^3. As shown in Figure 3, compound the compound of Example 96 exhibited dose-dependant effects *in vivo*, with tumor growth inhibition observed for 25 mg/kg (67%), and 50 mg/kg (96%). Significant tumor growth inhibition was also observed for 100 mg/kg once daily (88%).

[0284] While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

CLAIMS

1. A compound of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



II

wherein,

Y is cyclohexyl, substituted with one to three substituents;

R_1 is hydrogen, $-NH_2$, or halo;

R_{12} independently at each occurrence is selected from the group consisting of hydrogen, and halo; and

R_5 is selected from cyclohexyl, phenyl, and pyridyl, wherein said cyclohexyl, said phenyl, and said pyridyl are each independently substituted with up to three substituents selected from halo, hydroxyl, C_{1-4} alkyl, and OC_{1-4} alkyl.

2. A compound of Claim 1 wherein Y is substituted with one to three substituents selected from hydroxyl, amino, C_{1-4} alkyl, and C_{1-4} halo alkyl.

3. A compound of Claim 2 wherein Y is substituted with one to three substituents selected from methyl, hydroxyl, amino, and CF_3.

4. A compound of Claim 2 wherein R_1 is hydrogen, amino, or fluoro.

5. A compound of Claim 2 wherein R_5 is pyridyl or phenyl.

6. A compound of Claim 5 wherein R_5 is phenyl substituted with up to three substituents selected from halo, hydroxyl, alkoxy, and C_{1-4} alkyl.

7. A compound of Claim 5 wherein Y is substituted with one to three substituents selected from methyl, hydroxyl, amino, and CF_3; R_1 is hydrogen; and R_5 is

phenyl substituted with up to three substituents selected from fluoro, hydroxyl, methyl, ethyl, methoxy, and propoxy.

8. A compound of Claim 7 wherein R_1 is 2,6-difluorophenyl.

9. A compound of Claim 1, selected from the group consisting of

N-(4-((3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide;

3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)picolinamide;

N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide;

3-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide; and

N-(4-((3S)-3-aminocyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of any of Claim 1 to Claim 9.

11. A pharmaceutical composition comprising a compound of any of Claim 1 to Claim 9, wherein said pharmaceutical composition comprises an additional agent for the treatment of cancer.

12. A pharmaceutical composition of Claim 11 wherein the additional agent is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, and trastuzumab.

13. A use of a compound of any of Claim 1 to Claim 9 for preparing a medicament for treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity .

102

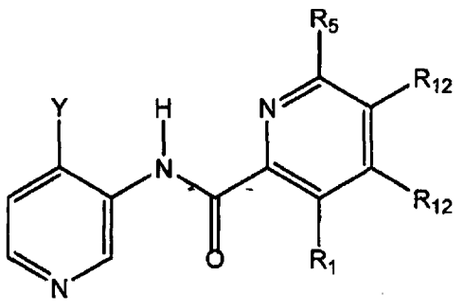
14. The use of Claim 13 wherein the condition is a cancer selected from carcinoma of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma and erythro leukemia, villous colon adenoma, and osteosarcoma.

15. A compound of Claim 1 to 9 for use in treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity .

16. The compound of Claim 15 wherein the condition is a cancer selected from carcinoma of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma and erythro leukemia, villous colon adenoma, and osteosarcoma.

17. A compound of Formula II selected from Table I or Table II.

18. A compound of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



II

wherein,

Y is piperidinyl substituted with methyl, hydroxyl, and amino;

R_1 is selected from the group consisting of hydrogen, NH_2, and fluoro;

R_{12} independently at each occurrence is selected from the group consisting of hydrogen, and halo; and

R_5 is selected from pyridyl, fluoro pyridyl, cyclohexyl, and phenyl, wherein said phenyl is substituted up to three substituents selected from fluoro, hydroxyl, and methyl.

19. A compound of Claim 18 wherein Y represents 3-amino-4-hydroxy-5-methylpiperidin-1-yl.

20. A compound of Claim 18 or 19 wherein R_1 is hydrogen.

21. A compound of Claim 20 wherein R_5 is difluoro phenyl.

22. A compound of Claim 18 or Claim 19 wherein R_5 is 2,6-difluoro phenyl.

23. A compound of Claim 18 selected from N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide, and N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-6-(2,6-difluoro-3-methylphenyl)-5-fluoropicolinamide.

24. A pharmaceutical composition comprising a compound of Claim 18 or Claim 23, wherein said pharmaceutical composition comprises at least one additional agent for the treatment of cancer.

25. The pharmaceutical composition of Claim 24 wherein the additional agent is selected from the group consisting of irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, and trastuzumab.

26. A use of a compound of Claim 18 for preparing a medicament for treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity .

27. The use of Claim 26 wherein the condition is a cancer selected from carcinoma of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma and erythro leukemia, villous colon adenoma, and osteosarcoma.

28. A compound of Claim 18 to 23 for use in treating a condition by modulation of Provirus Integration of Maloney Kinase (PIM Kinase) activity .

29. The compound of Claim 28 wherein the condition is a cancer selected from carcinoma of the lungs, pancreas, thyroid, ovarian, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma and erythro leukemia, villous colon adenoma, and osteosarcoma.

28. A compound of Formula II selected from Table I or Table II.

Example 99 (P.O.)

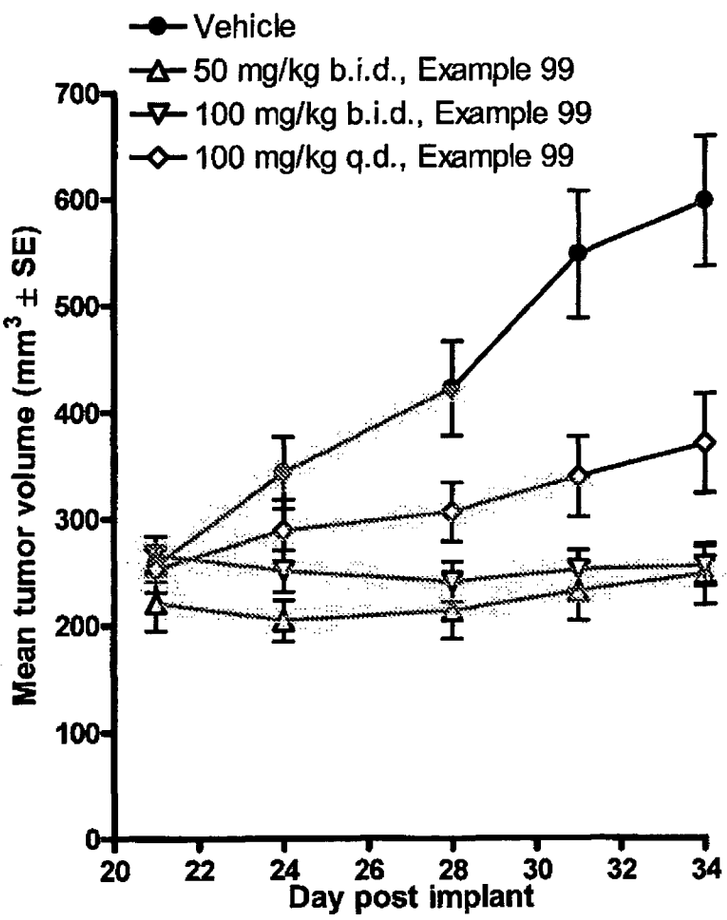


Figure 1

Example 70 (P.O.)

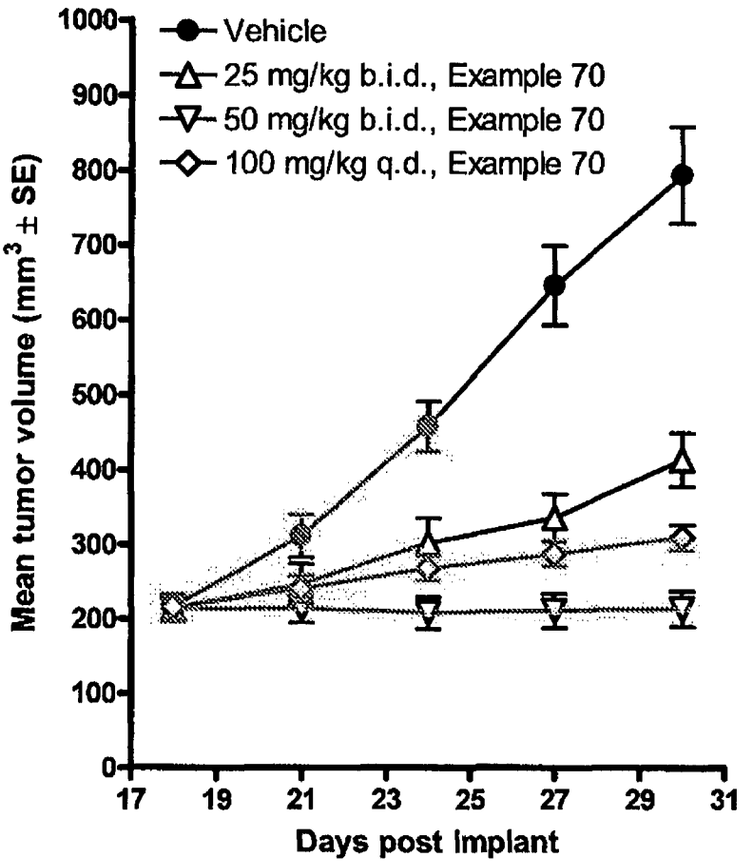


Figure 2

Example 96 (P.O.)

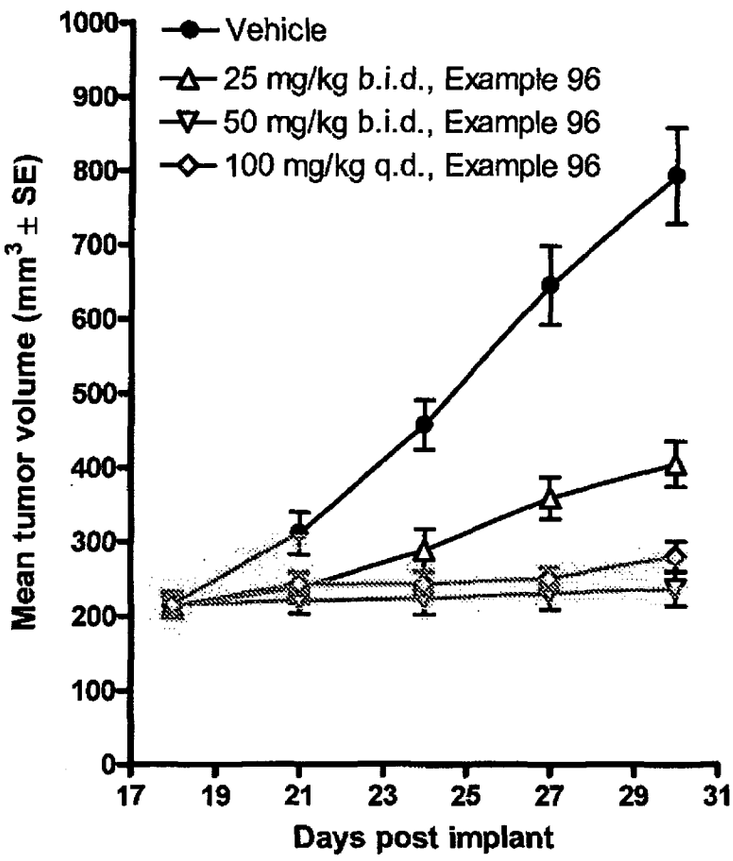


Figure 3

105

DERIVADOS DE PICOLINAMIDA COMO INHIBIDORES DE CINASA

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

Esta solicitud reclama el beneficio de acuerdo con 35 U.S.C. §119(e) para la solicitud provisional de E.U.A. Serie No. 61/093,666, presentada el 2 de Septiembre del 2008, y solicitud provisional de E.U.A. Serie No. 61/225,660, presentada el 15 de Julio del 2009, las cuales se incorporan aquí en su totalidad para referencia.

CAMPO DE LA INVENCION

La presente invención se refiere a nuevos compuestos y a sus tautómeros y estereoisómeros, y a las sales farmacéuticamente aceptables, ésteres, metabolitos o pro-fármacos de los mismos, a composiciones de los nuevos compuestos junto con vehículos farmacéuticamente aceptables, y al uso de los nuevos compuestos, ya sea solos o bien en combinación con cuando menos un agente terapéutico adicional, en la profilaxis o en el tratamiento de cáncer.

ANTECEDENTES

La infección con el retrovirus Maloney y la integración del genoma en el genoma de la célula huésped da como resultado el desarrollo de linfomas en ratones. La integración del

provirus de la cinasa Maloney (Cinasa-PIM) se identificó como uno de los proto-oncogenes frecuentes capaces de activarse transcripcionalmente mediante este evento de integración de retrovirus (Cuypers H.T. y colaboradores, "Murine leukemia virus-induced T-cell limphoma-genesis: integration of proviruses in a distinct chromosomal region", *Cell* 37(1): 141-50 (1984); Selten G. y colaboradores, "Proviral activation of the putative oncogene Pim-1 in MuLV induced T-cell limphomas" *EMBO J* 4(7): 1793-8 (1985)), estableciendo por consiguiente una correlación entre la sobre-expresión de esta cinasa y su potencial oncogénico. El análisis de homología de secuencias demostró que hay 3 Cinasas-Pim altamente homólogas (Pim1, 2 y 3), siendo Pim1 el proto-oncogén originalmente identificado por la integración del retrovirus. Adicionalmente, los ratones transgénicos que sobre-expresan Pim1 o Pim2 muestran una mayor incidencia de linfomas de células-T (Breuer M y colaboradores, "Very high frequency of limphoma induction by a chemical carcinogen in pim-1 transgenic mice" *Nature* 340(6228): 61-3 (1989)), mientras que la sobre-expresión en conjunto con c-myc está asociada con la incidencia de linfomas de células-B (Verbeek S y colaboradores, "Mice bearing the E mu-myc and E mu-pim-1 transgenes develop pre-B-cell leukemia prenatally" *Mol Cell Biol* 11(2): 1176-9 (1991)). Por consiguiente, estos modelos animales establecen una fuerte correlación entre la sobre-expresión de Pim y la oncogénesis

en las malignidades hematopoiéticas. En adición a estos modelos animales, se ha reportado la sobre-expresión de Pim en muchas otras malignidades humanas. Con frecuencia se observa la sobre-expresión de Pim1, 2 y 3 en muchas malignidades hematopoiéticas (Amson R y colaboradores, "The human protooncogene product p33pim is expressed during fetal hematopoiesis and in diverse leukemias", *PNAS EUA* 86(22): 8857-61 (1989); Cohen AM y colaboradores, "Increased expression of the hPim-2 gene in human chronic lymphocytic leukaemia and non-Hodgkin limphoma," *Leuk Lymph* 45(5): 951-5 (2004), Huttmann A y colaboradores, "Gene expression signatures separate B-cell chronic lymphocytic leukaemia prognostic subgroups defined by ZAP-70 and CD38 expression status," *Leukaemia* 20: 1774–1782 (2006)), y en cáncer de próstata (Dhanasekaran SM y colaboradores, "Delineation of prognostic biomarkers in prostate cancer", *Nature* 412(6849): 822-6 (2001); Cibull TL y colaboradores, "Over-expression of Pim-1 during progress of prostatic adenocarcinoma", *J Clin Pathol* 59(3): 285-8 (2006)), mientras que con frecuencia se observa la sobre-expresión de Pim3 en el carcinoma hepatocelular (Fujii C y colaboradores, "Aberrant expression of serine/threonine kinase Pim-3 in hepatocellular carcinoma development and its role in the proliferation of human hepatoma cell lines," *Int J Cancer* 114: 209–218 (2005)), y cáncer pancreático (Li YY y colaboradores, "Pim-3, a proto-oncogene

with serine/threonine kinase activity, is aberrantly expressed in human pancreatic cancer and phosphorylates bad to block bad-mediated apoptosis in human pancreatic cancer cell lines", *Cancer Res* 66(13): 6741-7 (2006)).

Pim1, 2 y 3 son cinasas de serina/treonina que normalmente funcionan en la sobrevivencia y proliferación de las células hematopoiéticas en respuesta a los factores de crecimiento y las citoquinas. Las citoquinas que señalizan a través de la senda de Jak/Stat conducen a la activación de la transcripción de los genes Pim y a la síntesis de las proteínas. No se requieren más modificaciones posteriores a la traducción para la actividad de la Cinasa-Pim. Por consiguiente, la señalización corriente abajo es primordialmente controlada en el nivel de la transcripción/traducción y del cambio de proteína. Los sustratos para las Cinasas-Pim incluyen reguladores de apoptosis, tales como el miembro de la familia Bcl-2, BAD (Aho T y colaboradores, "Pim-1 kinase promotes inactivation of the pro-apoptotic Bad protein by phosphorylating it on the SeR_{112} gatekeeper site": *FEBS Letters* 571: 43–49 (2004)), los reguladores del ciclo celular, tales como $p21^{WFA1/CIP1}$ (Wang Z, y colaboradores, "Phosphorylation of cell cycle inhibitor p21Cip1/WAF1 by Pim-1 kinase", *Biochem Biophys Acta* 1593: 45–55 (2002)), CDC25A (1999), C-TAK (Bachmann M y colaboradores, "The Oncogenic Serine/Threonine Kinase Pim-1 Phosphorylates and Inhibits the Activity of Cdc25C-associated

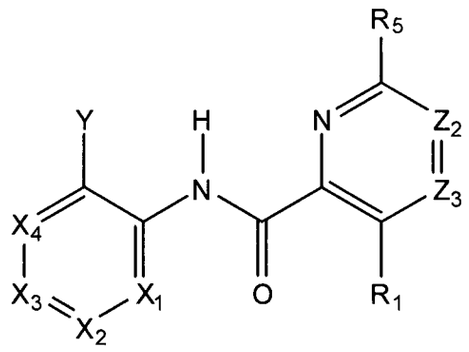
Kinase 1 (C-TAK1). A novel role for Pim-1 at the G2/M cell cycle checkpoint", *J Biol Chem* 179: 48319-48328 (2004)) y NuMA (Bhattacharya N, y colaboradores, "Pim-1 associates with protein complexes necessary for mithosis, "*Chromosoma* 111(2):80-95 (2002)), y el regulador de la síntesis de proteínas 4EBP1 (Hammerman PS y colaboradores, "Pim and Akt oncogenes are independent regulators of hematopoietic cell growth and survival," Blood 105(11): 4477-83 (2005)). Los efectos de las Pim(s) en estos reguladores son consistentes con un papel en la protección de la apoptosis, y en la promoción de la proliferación y el crecimiento celular. Por consiguiente, se piensa que la sobre-expresión de Pim(s) en el cáncer tiene un papel en la promoción de la sobrevivencia y proliferación de las células de cáncer y, por consiguiente, su inhibición debería ser una manera efectiva de tratar los cánceres en los que se sobre-expresan. De hecho, varios reportes indican que la eliminación genética de la expresión de Pim(s) con el siARN, da como resultado la inhibición de la proliferación y muerte celular (Dai JM, y colaboradores, "Antisense oligodeoxynucleotides targeting the serine / threonine kinase Pim-2 inhibited proliferation of DU-145 cells", *Acta Pharmacol Sin* 26(3): 364-8 (2005); Fujii y colaboradores 2005; Li y colaboradores 2006). Adicionalmente, se piensa que la activación mutacional de varios oncogenes bien conocidos en las malignidades hematopoiéticas ejerce sus efectos cuando

menos en parte a través de Pim(s). Por ejemplo, la sub-regulación dirigida de la expresión de Pim perjudica la sobrevivencia de las células hematopoiéticas transformadas por Flt3 y BCR/ABL (Adam y colaboradores 2006). Por consiguiente, los inhibidores para Pim1, 2 y 3 serían útiles en el tratamiento de estas malignidades. En adición a un papel potencial en el tratamiento de cáncer y de las enfermedades mielo-proliferativas, este inhibidor podría ser útil para controlar la expansión de las células inmunes en otras condiciones patológicas, tales como enfermedades autoinmunes, reacciones alérgicas, y en los síndromes de rechazo de trasplantes de órganos. Esta noción es apoyada por los hallazgos de que la diferenciación de las células-T auxiliares Th1 mediante IL-12 e IFN-α, da como resultado la inducción de expresión de ambas Pim1 y 2 (Aho T y colaboradores, "Expression of human Pim family genes is selectively up-regulated by cytokines promoting T helper type 1, but not T helper type 2, cell differentiation", *Immunology* 116: 82-88 (2005)). Más aún, la expresión de Pim(s) es inhibida en ambos tipos de células por el TGF-ß inmunosupresor (Aho y colaboradores 2005). Estos resultados sugieren que las cinasas Pim están involucradas en el proceso de diferenciación temprana de las células-T auxiliares, las cuales coordinan las respuestas inmunológicas en las enfermedades autoinmunes, reacción alérgica, y rechazo de trasplante de tejido.

Existe una necesidad continua de compuestos que inhiban la proliferación de capilares, que inhiban el crecimiento de tumores, que traten el cáncer, que modulen el paro del ciclo celular, y/o que inhiban las moléculas tales como Pim1, Pim2, y Pim3, y de formulaciones farmacéuticas y medicamentos que contengan estos compuestos. También existe una necesidad de métodos para la administración de estos compuestos, formulaciones farmacéuticas, y medicamentos para los pacientes o sujetos que los necesiten.

BREVE DESCRIPCION DE LA INVENCION

Se proporcionan nuevos compuestos, y sus estereoisómeros, tautómeros, y sales farmacéuticamente aceptables, de la fórmula I:



I

en donde:

X_1, X_2, X_3 y X_4 se seleccionan independientemente a partir de CR_2 y N; en el entendido de que cuando menos uno pero no más de dos de X_1, X_2, X_3 y X_4 son N;

Y se selecciona a partir de un grupo que consiste en cicloalquilo, cicloalquilo parcialmente insaturado, y hetero-cicloalquilo, en donde cada miembro de este grupo puede estar sustituido con hasta cuatro sustituyentes;

Z_2 y Z_3 se seleccionan independientemente a partir de CR_{12} y N; en el entendido de que no más de uno de Z_2 y Z_3 puede ser N;

R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NHR_3$, halógeno, hidroxilo, alquilo, ciano, y nitro;

R_2 y R_{12}, independientemente en cada presentación, se seleccionan a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, nitro, ciano, SO_3H, y alquilo sustituido o insustituido, alquenilo, alquinilo, alcoxilo, amino, cicloalquilo, hetero-cicloalquilo, y cicloalquilo parcialmente saturado;

R_3 se selecciona a partir del grupo que consiste en hidrógeno, $-CO-R_4$ y alquilo sustituido o insustituido, cicloalquilo, heterociclilo, arilo, y heteroarilo;

R_4 se selecciona a partir del grupo que consiste en alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, amino, amino sustituido, y alquil-amino; y

R_5 representa un grupo seleccionado a partir de arilo sustituido o insustituido, cicloalquilo de 3 a 7 átomos de carbono, heteroarilo, cicloalquilo parcialmente insaturado, y alquilo, en donde cada grupo R_5 sustituido mencionado puede estar sustituido con hasta cuatro sustituyentes seleccionados a

partir de halógeno, ciano, amino, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, alcoxilo, nitro, carboxilo, carbonilo, carboalcoxilo, amino-carboxilo, amino-carbonilo sustituido, amino-sulfonilo, amino-sulfonilo sustituido, y alcoxi-alquilo.

En algunas modalidades, se proporcionan nuevos compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde X_2 es N, y X_1, X_3 y X_4 son CR_2.

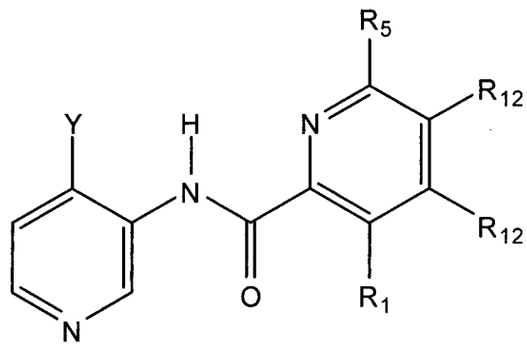
En algunas modalidades, se proporcionan nuevos compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_2 se selecciona a partir de hidrógeno, metilo, etilo, halógeno, ciano.

En algunas modalidades, se proporcionan compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Z_2 y Z_3 son CR_{12}.

En algunas modalidades, se proporcionan compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_{12} se selecciona a partir de hidrógeno, halógeno, metilo, etilo, y ciano.

En otras modalidades, se proporcionan nuevos compuestos, y sus estereoisómeros, tautómeros, y las sales

farmacéuticamente aceptables, de la fórmula II:



II

en donde:

Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexilo parcialmente insaturado, y hetero-ciclo-alquilo de 5 átomos de carbono, en donde cada miembro de este grupo puede estar sustituido con hasta cuatro sustituyentes;

R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NHR_3$, halógeno, hidroxilo, alquilo, cicloalquilo de 3 a 4 átomos de carbono, ciano, y nitro;

R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, amino, nitro, ciano, SO_3H, y alquilo sustituido o insustituido, alquenilo, alquinilo, alcoxilo, amino, cicloalquilo, hetero-cicloalquilo, y cicloalquilo parcialmente saturado;

R_3 se selecciona a partir del grupo que consiste en hidrógeno, $-CO-R_4$ y alquilo sustituido o insustituido,

cicloalquilo, heterociclilo, arilo, y heteroarilo;

R_4 se selecciona a partir del grupo que consiste en alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, amino, amino sustituido, y alquil-amino; y

R_5 representa un grupo seleccionado a partir de hidrógeno y alquilo sustituido o insustituido, cicloalquilo de 6 átomos de carbono, arilo, y heteroarilo, en donde cada grupo R_5 sustituido mencionado puede estar sustituido con hasta cuatro sustituyentes seleccionados a partir de halógeno, ciano, amino, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, alcoxilo, nitro, carboxilo, carbonilo, carboalcoxilo, amino-carboxilo, amino-carbonilo sustituido, amino-sulfonilo, amino-sulfonilo sustituido, y alcoxi-alquilo.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en cicloalquilo, cicloalquenilo, piperidinilo y piperazinilo sustituidos o insustituidos, en donde cada miembro de este grupo está sustituido con hasta cuatro sustituyentes. En algunas modalidades, Y está sustituido con hasta cuatro sustituyentes seleccionados a partir de ciano, nitro, halógeno, hidroxilo, amino, alcoxilo, amino sustituido, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 4 átomos de carbono. En todavía otras modalidades, Y

está sustituido con hasta cuatro sustituyentes seleccionados a partir de metilo, propilo, isopropilo, etilo, hidroxilo, amino, halógeno, mono-halo-alquilo de 1 a 3 átomos de carbono, tri-halo-alquilo de 1 a 3 átomos de carbono, y di-halo-alquilo de 1 a 3 átomos de carbono.

En algunas modalidades, se proporcionan nuevos compuestos de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexinilo, y piperidinilo sustituidos o insustituidos, en donde cada miembro de este grupo está sustituido con hasta cuatro sustituyentes.

En algunas modalidades, se proporcionan nuevos compuestos de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y está sustituido con hasta cuatro sustituyentes seleccionados independientemente a partir de hidrógeno, ciano, nitro, halógeno, hidroxilo, amino, alcoxilo, amino sustituido, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 4 átomos de carbono. En algunas modalidades, los sustituyentes se seleccionan independientemente a partir de metilo, propilo, isopropilo, etilo, hidroxilo, amino, halógeno, mono-halo-alquilo de 1 a 3 átomos de carbono, tri-halo-alquilo de 1 a 3 átomos de carbono, y di-halo-alquilo de 1 a 3 átomos de carbono.

En algunas modalidades, se proporcionan compuestos de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_{12} se selecciona a partir de hidrógeno, halógeno, metilo, etilo, y ciano.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir del grupo que consiste en ciclohexilo sustituido o insustituido, ciclohexenilo, piperidinilo, piperazinilo, en donde el grupo Y mencionado puede estar sustituido con hasta tres sustituyentes seleccionados a partir de metilo, etilo, hidroxilo, amino, y metoxilo; R_1 se selecciona a partir del grupo que consiste en hidrógeno, y amino; y R_{12}, independientemente en cada presentación, representa hidrógeno, halógeno, o metilo.

En algunas modalidades, se proporcionan compuestos de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexenilo, piperidinilo, y piperazinilo sustituidos; R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NH_2$, halógeno, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 4 átomos de carbono, y -CN; R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que

consiste en hidrógeno, halógeno, alquilo de 1 a 4 átomos de carbono, y amino; y R_5 se selecciona a partir del grupo que consiste en fenilo sustituido o insustituido, ciclohexilo, ciclopentilo, tiazol, piridilo, pirimidilo y pirazinilo, en donde el grupo R_5 puede estar sustituido con hasta tres sustituyentes seleccionados a partir de halógeno, hidrógeno, metilo, amino-carbonilo sustituido, y alcoxilo.

En una modalidad representativa, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, seleccionados a partir del grupo que consiste en N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, y N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, y 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida.

En otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con la integración del provirus de la cinasa Maloney (Cinasa PIM)

en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto una cantidad de un compuesto de la fórmula I o II efectiva para inhibir la actividad de PIM en el sujeto.

En otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con PIM en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto una cantidad de un compuesto de la fórmula I o II efectiva para reducir o prevenir el crecimiento tumoral en el sujeto.

En todavía otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con PIM en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto una cantidad de un compuesto de la fórmula I o II efectiva para reducir o prevenir el crecimiento tumoral en el sujeto, en combinación con cuando menos un agente adicional para el tratamiento de cáncer.

En todavía otros aspectos, la presente invención proporciona composiciones terapéuticas que comprenden cuando menos un compuesto de la fórmula I o II en combinación con uno o más agentes adicionales para el tratamiento de cáncer, como se emplean comúnmente en la terapia de cáncer.

Los compuestos de la invención son útiles en el

tratamiento de cánceres, incluyendo malignidades hematopoiéticas, carcinomas (por ejemplo, de los pulmones, hígado, páncreas, ovarios, tiroides, vejiga, o colon), melanoma, trastornos mieloides (por ejemplo, leucemia mieloide, mieloma múltiple, y eritroleucemia), adenomas (por ejemplo, adenoma de colon velloso), sarcomas (por ejemplo, osteosarcoma), enfermedades autoinmunes, reacciones alérgicas, y en los síndromes de rechazo de trasplantes de órganos.

La invención proporciona además composiciones, métodos de uso, y métodos de fabricación como se describen en la Descripción Detallada de la Invención.

DESCRIPCION DE LOS DIBUJOS

Los aspectos anteriores y muchas de las ventajas aunadas de esta invención llegarán a ser más fácilmente apreciadas a medida que las mismas lleguen a ser mejor entendidas haciendo referencia a la siguiente descripción detallada, al tomarse en conjunto con los dibujos acompañantes, en donde:

La Figura 1 es una gráfica que muestra la eficacia del compuesto del Ejemplo 99 a partir de una evaluación en el modelo de xeno-injerto KMS11-luc, como se describe en el Ejemplo 144.

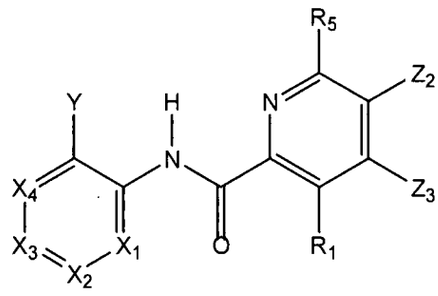
La Figura 2 es una gráfica que muestra la eficacia del compuesto del Ejemplo 70 a partir de una evaluación en el

modelo de xeno-injerto KMS11-luc, como se describe en el Ejemplo 144.

La Figura 3 es una gráfica que muestra la eficacia del compuesto del Ejemplo 96 a partir de una evaluación en el modelo de xeno-injerto KMS11-luc, como se describe en el Ejemplo 144.

DESCRIPCION DETALLADA

De acuerdo con un aspecto de la presente invención, se proporcionan nuevos compuestos, y sus estereoisómeros, tautómeros, y sales farmacéuticamente aceptables, de la fórmula I:



I

en donde:

X_1, X_2, X_3 y X_4 se seleccionan independientemente a partir de CR_2 y N; en el entendido de que cuando menos uno pero no más de dos de X_1, X_2, X_3 y X_4 son N;

Y se selecciona a partir de un grupo que consiste en cicloalquilo, cicloalquilo parcialmente insaturado, y hetero-cicloalquilo, en donde cada miembro de este grupo puede estar

sustituido con hasta cuatro sustituyentes;

Z_2 y Z_3 se seleccionan independientemente a partir de CR_{12} y N; en el entendido de que no más de uno de Z_2 y Z_3 puede ser N;

R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NHR_3$, halógeno, hidroxilo, alquilo, ciano, y nitro;

R_2 y R_{12}, independientemente en cada presentación, se seleccionan a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, nitro, ciano, SO_3H, y alquilo sustituido o insustituido, alquenilo, alquinilo, alcoxilo, amino, cicloalquilo, hetero-cicloalquilo, y cicloalquilo parcialmente saturado;

R_3 se selecciona a partir del grupo que consiste en hidrógeno, $-CO-R_4$ y alquilo sustituido o insustituido, cicloalquilo, heterociclilo, arilo, y heteroarilo;

R_4 se selecciona a partir del grupo que consiste en alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, amino, amino sustituido, y alquil-amino; y

R_5 representa un grupo seleccionado a partir de arilo sustituido o insustituido, cicloalquilo de 3 a 7 átomos de carbono, heteroarilo, cicloalquilo parcialmente insaturado, y alquilo, en donde cada grupo R_5 sustituido mencionado puede estar sustituido con hasta cuatro sustituyentes seleccionados a partir de halógeno, ciano, amino, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, alcoxilo, nitro, carboxilo, carbonilo, carboalcoxilo, amino-carboxilo,

amino-carbonilo sustituido, amino-sulfonilo, amino-sulfonilo sustituido, y alcoxi-alquilo.

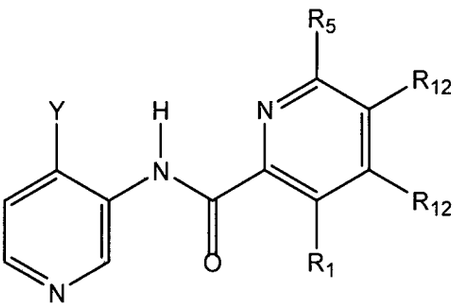
En algunas modalidades, se proporcionan nuevos compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde X_2 es N, y X_1, X_3 y X_4 son CR_2.

En algunas modalidades, se proporcionan nuevos compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_2 se selecciona a partir de hidrógeno, metilo, etilo, halógeno, ciano.

En algunas modalidades, se proporcionan compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Z_2 y Z_3 son CR_{12}.

En algunas modalidades, se proporcionan compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_{12} se selecciona a partir de hidrógeno, halógeno, metilo, etilo, y ciano.

En otras modalidades, se proporcionan nuevos compuestos, y sus estereoisómeros, tautómeros, y las sales farmacéuticamente aceptables, de la fórmula II:



II

en donde:

Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexilo parcialmente insaturado, y hetero-ciclo-alquilo de 5 átomos de carbono, en donde cada miembro de este grupo puede estar sustituido con hasta cuatro sustituyentes;

R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NHR_3$, halógeno, hidroxilo, alquilo, cicloalquilo de 3 a 4 átomos de carbono, ciano, y nitro;

R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, amino, nitro, ciano, SO_3H, y alquilo sustituido o insustituido, alquenilo, alquinilo, alcoxilo, amino, cicloalquilo, hetero-cicloalquilo, y cicloalquilo parcialmente saturado;

R_3 se selecciona a partir del grupo que consiste en hidrógeno, $-CO-R_4$ y alquilo sustituido o insustituido, cicloalquilo, heterociclilo, arilo, y heteroarilo;

R_4 se selecciona a partir del grupo que consiste en

alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, amino, amino sustituido, y alquil-amino; y

R_5 representa un grupo seleccionado a partir de hidrógeno y alquilo sustituido o insustituido, cicloalquilo de 6 átomos de carbono, arilo, y heteroarilo.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en cicloalquilo, cicloalquenilo, piperidinilo y piperazinilo sustituidos o insustituidos, en donde cada miembro de este grupo está sustituido con hasta cuatro sustituyentes. En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexinilo, y piperidinilo sustituidos o insustituidos, en donde cada miembro de este grupo está sustituido con hasta cuatro sustituyentes. En algunas modalidades, Y está sustituido con hasta cuatro sustituyentes seleccionados a partir de hidrógeno, ciano, nitro, halógeno, hidroxilo, amino, alcoxilo, amino sustituido, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 4 átomos de carbono. En todavía otras modalidades, Y está sustituido con hasta cuatro sustituyentes seleccionados a partir de metilo,

propilo, isopropilo, etilo, hidroxilo, amino, halógeno, mono-halo-alquilo de 1 a 3 átomos de carbono, tri-halo-alquilo de 1 a 3 átomos de carbono, y di-halo-alquilo de 1 a 3 átomos de carbono.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_1 es hidrógeno, amino, o flúor. En una modalidad, se proporcionan los compuestos de la fórmula II seleccionados a partir del Cuadro I o del Cuadro II.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_5 se selecciona a partir de arilo sustituido o insustituido, cicloalquilo de 5 a 6 átomos de carbono, heteroarilo, cicloalquilo parcialmente insaturado de 5 a 6 átomos de carbono, y alquilo de 1 a 4 átomos de carbono, en donde cada grupo mencionado puede estar sustituido con hasta cuatro sustituyentes seleccionados a partir de halógeno, ciano, amino, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 5 átomos de carbono, alcoxilo, nitro, carboxilo, carbonilo, carboalcoxilo, amino-carboxilo, amino-carbonilo sustituido, amino-sulfonilo, amino-sulfonilo sustituido, y alcoxi-alquilo. En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal

farmacéuticamente aceptable de los mismos, en donde R_5 es fenilo sustituido o insustituido, en donde el grupo fenilo puede estar sustituido con hasta cuatro sustituyentes seleccionados a partir de hidrógeno, ciano, nitro, halógeno, hidroxilo, amino, alcoxilo, amino sustituido, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 4 átomos de carbono. En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_5 es 2,6-difluoro-fenilo.

En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde R_{12} se selecciona a partir de hidrógeno, halógeno, metilo, etilo, y ciano. En algunas modalidades, se proporcionan compuestos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir del grupo que consiste en ciclohexilo sustituido o insustituido, ciclohexenilo, piperidinilo, piperazinilo, en donde el grupo Y mencionado puede estar sustituido con hasta tres sustituyentes seleccionados a partir de metilo, etilo, hidroxilo, amino, y metoxilo; R_1 se selecciona a partir del grupo que consiste en hidrógeno, y amino; y R_{12}, independientemente en cada presentación, representa hidrógeno, halógeno, o metilo.

En algunas modalidades, se proporcionan compuestos de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde Y se selecciona a partir de un grupo que consiste en ciclohexilo, ciclohexenilo, piperidinilo, y piperazinilo sustituidos; R_1 se selecciona a partir del grupo que consiste en hidrógeno, $-NH_2$, halógeno, alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 4 átomos de carbono, y -CN; R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno, halógeno, alquilo de 1 a 4 átomos de carbono, y amino; y R_5 se selecciona a partir del grupo que consiste en fenilo sustituido o insustituido, ciclohexilo, ciclopentilo, tiazol, piridilo, pirimidilo y pirazinilo, en donde el grupo R_5 puede estar sustituido con hasta tres sustituyentes seleccionados a partir de halógeno, hidrógeno, metilo, amino-carbonilo sustituido, y alcoxilo.

Una modalidad preferida de la presente invención es un compuesto de la fórmula (II), en donde Y es ciclohexilo sustituido con uno a tres sustituyentes, siendo estos sustituyentes de preferencia seleccionados a partir de hidroxilo, amino, alquilo de 1 a 4 átomos de carbono o halo-alquilo de 1 a 4 átomos de carbono, y de una manera muy preferible, seleccionados a partir de metilo, hidroxilo, amino, y CF_3, y de una manera muy preferible a partir de metilo, amino, e hidroxilo; R_1 es hidrógeno, NH_2, o halógeno (de preferencia,

R_1 es hidrógeno, amino, o flúor, más preferiblemente, R_1 es hidrógeno); R_{12} son cada uno independientemente hidrógeno o halógeno (de preferencia, cada R_{12} es hidrógeno, cloro o flúor); R_5 es ciclohexilo, fenilo, o piridilo, en donde el ciclohexilo, fenilo, y piridilo mencionados están cada uno independientemente sustituidos con hasta tres sustituyentes seleccionados a partir de halógeno, hidroxilo, alquilo de 1 a 4 átomos de carbono, y alcoxilo de 1 a 4 átomos de carbono (de preferencia, R_5 es piridilo o fenilo, cada uno independientemente sustituido con hasta tres sustituyentes seleccionados a partir de halógeno, hidroxilo, alquilo de 1 a 4 átomos de carbono o alcoxilo de 1 a 4 átomos de carbono, más preferiblemente, R_5 es fenilo sustituido con hasta tres sustituyentes seleccionados a partir de halógeno, hidroxilo, alcoxilo de 1 a 4 átomos de carbono, y alquilo de 1 a 4 átomos de carbono, de una manera muy preferible, es fenilo sustituido con hasta tres sustituyentes seleccionados a partir de flúor, hidroxilo, metilo, etilo, metoxilo, o propoxilo, de una manera muy preferible, R_5 es 2,6-difluoro-fenilo.

Todavía otra modalidad preferida de la presente invención proporciona un compuesto de la fórmula II, en donde Y es piperidinilo sustituido con metilo, hidroxilo, y amino; R_1 es hidrógeno, NH_2, o flúor; R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno y halógeno; y R_5 es piridilo, fluoro-piridilo,

ciclohexilo, o fenilo, en donde el fenilo está sustituido con hasta tres sustituyentes seleccionados a partir de flúor, hidroxilo, y metilo, de preferencia R_5 es difluoro-fenilo. En una modalidad preferida adicional, de preferencia Y es 3-amino-4-hidroxi-5-metil-piperidin-1-ilo; R_1 es hidrógeno; y R_5 es 2,6-difluoro-fenilo.

En una modalidad representativa, los compuestos preferidos de las fórmulas I o II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, se seleccionan a partir del grupo que consiste en N-(4-((3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida; N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-

ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida); N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; y 3-amino-N-(4-((1R,3S)-3-amino-ciclo-hexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida.

En otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con la integración del provirus de la cinasa Maloney (Cinasa PIM) en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto una cantidad de un compuesto de la fórmula I o II efectiva para inhibir la actividad de PIM en el sujeto. Una modalidad preferida de la presente invención proporciona un método para el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM), el cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula I.

En otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con

PIM en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto, una cantidad de un compuesto de la fórmula I o II efectiva para reducir o prevenir el crecimiento tumoral en el sujeto. En todavía otros aspectos, la presente invención proporciona métodos para el tratamiento de los trastornos relacionados con PIM en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar a este sujeto, una cantidad de un compuesto de la fórmula I o II efectiva para reducir o prevenir el crecimiento tumoral en el sujeto, en combinación con cuando menos un agente adicional para el tratamiento de cáncer.

En todavía otro aspecto, la presente invención proporciona composiciones terapéuticas que comprenden cuando menos un compuesto de la fórmula I o II en combinación con uno o más agentes adicionales para el tratamiento de cáncer, como se emplean comúnmente en la terapia de cáncer. La presente invención por consiguiente, proporciona una composición farmacéutica, la cual comprende un compuesto de la fórmula I o de la fórmula II. Una modalidad preferida de este aspecto, proporciona una composición farmacéutica, la cual comprende un compuesto seleccionado a partir de N-(4-((3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-

il)-6-(2,6-difluoro-fenil)-picolinamida; N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida); N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; y N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida. Otra modalidad preferida proporciona una composición farmacéutica, la cual comprende además un agente adicional para el tratamiento de cáncer, en donde de

preferencia el agente adicional se selecciona a partir de irinotecano, topotecano, gemcitabina, 5-fluoro-uracilo, leucovorina, carboplatina, cisplatina, taxanos, tezacitabina, ciclofosfamida, alcaloides vinca, imatinib (Gleevec), antraciclinas, rituximab, y trastuzumab.

Los compuestos de la invención son útiles en el tratamiento de cánceres, incluyendo malignidades hematopoiéticas, carcinomas (por ejemplo, de los pulmones, hígado, páncreas, ovarios, tiroides, vejiga, o colon), melanoma, trastornos mieloides (por ejemplo, leucemia mieloide, mieloma múltiple, y eritroleucemia), adenomas (por ejemplo, adenoma de colon velloso), sarcomas (por ejemplo, osteosarcoma), enfermedades autoinmunes, reacciones alérgicas, y en los síndromes de rechazo de trasplantes de órganos.

En todavía otro aspecto de la presente invención, se proporciona un uso de un compuesto de la fórmula I o de la fórmula II, para la preparación de un medicamento para el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM). En una modalidad preferida de este aspecto de la invención, la condición es un cáncer seleccionado a partir de carcinoma de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon, melanoma, leucemia mieloide, mieloma múltiple, y eritroleucemia, adenoma de colon velloso, y osteosarcoma.

En otro aspecto, la presente invención se refiere a métodos para inhibir la actividad de cuando menos una cinasa seleccionada a partir del grupo que consiste en Pim1, Pim2 y Pim3, en un sujeto, o para el tratamiento de una condición biológica mediada por cuando menos una de Pim1, Pim2 y Pim3, en un sujeto humano o animal que necesite dicho tratamiento, los cuales comprenden administrar al sujeto cuando menos un compuesto de la fórmula I o II, en una cantidad efectiva para inhibir la cinasa en el sujeto. Los compuestos terapéuticos son útiles para el tratamiento de los pacientes con una necesidad de estos inhibidores (por ejemplo, aquéllos que sufren de un cáncer mediado por una señalización anormal del receptor de cinasa de serina/treonina).

DEFINICIONES

"Inhibidor de PIM" se utiliza en la presente para referirse a un compuesto que exhibe una IC_{50} con respecto a una actividad de la cinasa PIM de no más de aproximadamente 100 μM y más típicamente no más de aproximadamente 50 μM, como se mide en los ensayos de agotamiento de PIM descritos más adelante en la presente.

La frase "alquilo" se refiere a los grupos alquilo que no contienen átomos heterogéneos. Por consiguiente, la frase incluye grupos alquilo de cadena recta, tales como metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo,

undecilo, dodecilo y similares. La frase también incluye los isómeros de cadena ramificada de los grupos alquilo de cadena recta, incluyendo, pero no limitándose a, los siguientes, los cuales se proporcionan a manera de ejemplo: $-CH(CH_3)_2$, $-CH(CH_3)-(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)-(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)-(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)-(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)-(CH_2CH_3)$, y otros. Por consiguiente, la frase "grupos alquilo" incluye los grupos alquilo primarios, los grupos alquilo secundarios, y los grupos alquilo terciarios. Los grupos alquilo preferidos incluyen los grupos alquilo de cadena recta y ramificada que tienen de 1 a 12 átomos de carbono. Una definición preferida de "alquilo" se refiere a los grupos alquilo de 1 a 4 átomos de carbono de cadena recta, tales como metilo, etilo, propilo normal, y butilo normal. La definición preferida de "alquilo" también incluye a los grupos alquilo ramificados de 3 a 5 átomos de carbono, incluyendo $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $CH(CH_3)CH_2\ CH_2CH_3$, $CH(CH_3)CH(CH_3)_2$, $CH_2CH(CH_3)CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, y $CH(CH_2CH_3)_2$, etc.

El término "alquenilo" se refiere a los grupos alquilo como se definen anteriormente, en donde hay cuando menos un punto

de insaturación, es decir, en donde dos átomos de carbono adyacentes están unidos mediante un doble enlace. El término "alquinilo" se refiere a los grupos alquilo, en donde dos átomos de carbono adyacentes están unidos por un triple enlace. El término "alcoxilo" se refiere a -OR, en donde R es alquilo.

Como se utiliza en la presente, el término "halógeno" o "halo" se refiere a los grupos cloro, bromo, flúor y yodo. "Halo-alquilo" se refiere a un radical de alquilo sustituido con uno o más átomos de halógeno. El término "halo-alquilo", por consiguiente, incluye mono-halo-alquilo, di-halo-alquilo, tri-halo-alquilo, y similares. Los grupos mono-halo-alquilo representativos incluyen $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH(F)CH_3$, $-CH(Cl)CH_3$; los grupos di-halo-alquilo representativos incluyen $CHCl_2$, $-CHF_2$, $-CCl_2CH_3$, $-CH(Cl)CH_2Cl$, $-CH_2CHCl_2$, $-CH_2CHF_2$; los grupos tri-halo-alquilo representativos incluyen $-CCl_3$, $-CF_3$, $-CCl_2CH_2Cl$, $-CF_2CH_2F$, $-CH(Cl)CHCl_2$, $-CH(F)CHF_2$; y los grupos perhalo-alquilo representativos incluyen $-CCl_3$, $-CF_3$, $-CCl_2CCl_3$, $-CF_2CF_3$.

"Amino" se refiere en la presente al grupo $-NH_2$. El término "alquil-amino" se refiere en la presente al grupo –NRR' en donde R y R' se seleccionan cada uno independientemente a partir de hidrógeno o un alquilo inferior. El término "aril-amino" se refiere en la presente al grupo –NRR' en donde R es arilo, y R' es hidrógeno, un alquilo inferior, o un arilo. El término "aralquil-amino" se refiere en la presente al grupo –NRR' en

donde R es un aralquilo inferior, y R' es hidrógeno, un alquilo inferior, un arilo, o un aralquilo inferior. El término ciano se refiere al grupo –CN. El término nitro se refiere al grupo $-NO_2$.

El término "alcoxi-alquilo" se refiere al grupo $-alq_1$-O-alq_2 en donde alk_1 es alquilo o alquenilo, y alq_2 es alquilo o alquenilo. El término "alcoxilo inferior-alquilo" se refiere a un alcoxi-alquilo, en donde alq_1 es alquilo inferior o alquenilo inferior, y alq_2 es alquilo inferior o alquenilo inferior. El término "ariloxi-alquilo" se refiere al grupo –alquil-O-arilo. El término "aralcoxi-alquilo" se refiere al grupo -alquilenil-O-aralquilo, en donde aralquilo es un aralquilo inferior.

El término "amino-carbonilo" se refiere en la presente al grupo $-C(O)-NH_2$. "Amino-carbonilo sustituido" se refiere en la presente al grupo –C(O)-NRR' en donde R es alquilo inferior y R' es hidrógeno o un alquilo inferior. En algunas modalidades, R y R', junto con el átomo de nitrógeno unido a ellos, se pueden tomar juntos para formar un grupo "hetero-cicloalquil-carbonilo". El término "aril-amino-carbonilo" se refiere en la presente al grupo -C(O)-NRR' en donde R es un arilo, y R' es hidrógeno, alquilo inferior o arilo. "Aralquil-amino-carbonilo" se refiere en la presente al grupo –C(O)-NRR' en donde R es aralquilo inferior, y R' es hidrógeno, alquilo inferior, arilo, o aralquilo inferior.

"Amino-sulfonilo" se refiere en la presente al grupo $-S(O)_2-NH_2$. "Amino-sulfonilo sustituido" se refiere en la

presente al grupo $-S(O)_2$-NRR' en donde R es alquilo inferior y R' es hidrógeno o un alquilo inferior. El término "aralquil-amino-sulfonil-arilo" se refiere en la presente al grupo –aril-$S(O)_2$–NH-aralquilo, en donde el aralquilo es aralquilo inferior.

"Carbonilo" se refiere al grupo divalente –C(O)-. "Carboxilo" se refiere a –C(=O)–OH. "Alcoxi-carbonilo" se refiere al éster –C(=O)–O en donde R es alquilo. "Alcoxilo inferior-carbonilo" se refiere al éster –C(=O)–O en donde R es alquilo inferior. "Cicloalquiloxi-carbonilo" se refiere a –C(=O)–O en donde R es cicloalquilo.

"Cicloalquilo" se refiere a un sustituyente de alquilo carbocíclico mono- o poli-cíclico. Los grupos carbocicloalquilo son los grupos cicloalquilo en donde todos los átomos del anillo son de carbono. Los sustituyentes típicos de cicloalquilo tienen de 3 a 8 átomos de la estructura base (es decir, del anillo), en donde cada átomo de la estructura base es carbono, o un átomo heterogéneo. El término "hetero-cicloalquilo" se refiere en la presente a los sustituyentes de cicloalquilo que tienen de 1 a 5, y más típicamente de 1 a 4 átomos heterogéneos en la estructura del anillo. Los átomos heterogéneos adecuados empleados en los compuestos de la presente invención son nitrógeno, oxígeno, y azufre. Las fracciones de hetero-cicloalquilo representativas incluyen, por ejemplo, morfolino, piperazinilo, piperidinilo, y similares. Los grupos

carbocicloalquilo son los grupos cicloalquilo en donde todos los átomos del anillo son de carbono. Cuando se utilizan en relación con sustituyentes de cicloalquilo, el término "policíclico" se refiere en la presente a las estructuras cíclicas de alquilo fusionadas y no fusionadas. Los términos "cicloalquilo parcialmente insaturado", "cicloalquilo parcialmente saturado", y "cicloalquenilo" se refieren todos a un grupo cicloalquilo en donde hay cuando menos un punto de insaturación, es decir, en donde los átomos adyacentes del anillo están conectados mediante un doble enlace o un triple enlace. Los ejemplos ilustrativos incluyen ciclohexinilo, cicloheptinilo, ciclopropenilo, ciclobutinilo, y similares.

Los términos "heterociclo sustituido", "grupo heterocíclico" o "heterociclo", como se utilizan en la presente, se refieren a cualquier anillo de 3 ó 4 miembros que contiene un átomo heterogéneo seleccionado a partir de nitrógeno, oxígeno, y azufre, o un anillo de 5 ó 6 miembros que contiene de uno a tres átomos heterogéneos seleccionados a partir del grupo que consiste en nitrógeno, oxígeno, o azufre; en donde el anillo de 5 miembros tiene de 0 a 2 dobles enlaces, y el anillo de 6 miembros tiene de 0 a 3 dobles enlaces; en donde los átomos de nitrógeno y azufre pueden estar opcionalmente oxidados; en donde los átomos heterogéneos de nitrógeno y azufre pueden ser opcionalmente cuaternizados; e incluyendo cualquier grupo bicíclico en donde cualquiera de los anillos

heterocíclicos anteriores se fusione con un anillo de benceno o con otro anillo heterocíclico de 5 ó 6 miembros independientemente definido anteriormente. El término "hetero-cicloalquilo", como se utiliza en la presente, se refiere a un anillo de 5 ó 6 miembros que contiene de uno a tres átomos heterogéneos seleccionados a partir del grupo que consiste en nitrógeno, oxígeno, o azufre, en donde el anillo no tiene dobles enlaces. Por ejemplo, el término "hetero-ciclo-alquilo de 5 átomos de carbono" se refiere a un anillo de 6 miembros que contiene 5 átomos de carbono, y un átomo heterogéneo, tal como N. El término "heterociclo", por consiguiente, incluye anillos, en donde el átomo heterogéneo es nitrógeno, así como los anillos parcialmente y completamente saturados. Los heterociclos preferidos incluyen, por ejemplo: diazapinilo, pirrilo, pirrolinilo, pirrolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, piridilo, piperidinilo, pirazinilo, piperazinilo, N-metil-piperazinilo, azetidinilo, N-metil-azetidinilo, pirimidinilo, piridazinilo, oxazolilo, oxazolidinilo, isoxazolilo, isoazolidinilo, morfolinilo, tiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, furilo, tienilo, triazolilo y benzotienilo.

Las fracciones heterocíclicas pueden estar insustituidas o mono-sustituidas o di-sustituidas o tri-sustituidas con diferentes sustituyentes seleccionados independientemente a

partir de hidroxilo, halógeno, oxo (C=O), alquil-imino (RN=, en donde R es un grupo alquilo inferior o alcoxilo inferior), amino, alquil-amino, dialquil-amino, acil-amino-alquilo, alcoxilo, tioalcoxilo, polialcoxilo, alquilo inferior, cicloalquilo, o halo-alquilo.

Los grupos heterocíclicos se pueden unir en diferentes posiciones, como será evidente para aquéllos que tengan experiencia en la técnica de la química orgánica y medicinal, en conjunto con la divulgación de la presente.

Los heterocíclicos representativos incluyen, por ejemplo, imidazolilo, piridilo, piperazinilo, piperidinilo, azetidinilo, tiazolilo, furanilo, triazolilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, indolilo, naftpiridinilo, indazolilo, y quinolizinilo.

"Arilo" se refiere a grupos aromáticos monocíclicos y policíclicos opcionalmente sustituidos que tienen de 3 a 14 átomos de carbono o átomos heterogéneos de la estructura base, e incluye tanto los grupos arilo carbocíclicos como los grupos arilo heterocíclicos. Los grupos arilo carbocíclicos son los grupos arilo en donde todos los átomos del anillo en el anillo aromático son de carbono. El término "hetero-arilo" se refiere en la presente a los grupos arilo que tienen de 1 a 4 átomos heterogéneos como átomos del anillo en un anillo aromático siendo el resto de los átomos del anillo átomos de

carbono. Cuando se utilizan en relación con los sustituyentes de arilo, el término "arilo policíclico" se refiere en la presente a las estructuras cíclicas fusionadas y no fusionadas, en donde cuando menos una estructura cíclica es aromática, tales como, por ejemplo, benzodioxozol (el cual tiene una estructura heterocíclica fusionada con un grupo fenilo, es decir, naftilo, y similares. Las fracciones de arilo de ejemplo empleadas como sustituyentes en los compuestos de la presente invención incluyen fenilo, piridilo, pirimidinilo, tiazolilo, indolilo, imidazolilo, oxadiazolilo, tetrazolilo, pirazinilo, triazolilo, tiofenilo, furanilo, quinolinilo, purinilo, naftilo, benzotiazolilo, benzopiridilo, y bencimidazolilo, y similares.

"Opcionalmente sustituido" o "sustituido" se refiere al reemplazo de uno o más átomos de hidrógeno con un radical monovalente o divalente. Los grupos de sustitución adecuados incluyen, por ejemplo, hidroxilo, nitro, amino, imino, ciano, halógeno, tio, sulfonilo, tioamido, amidino, imidino, oxo, oxamidino, metoxamidino, imidino, guanidino, sulfonamido, carboxilo, formilo, alquilo inferior, halo-alquilo inferior, alquilo inferior-amino, halo-alquilo inferior-amino, alcoxilo inferior, halo-alcoxilo inferior, alcoxilo inferior-alquilo, alquil-carbonilo, amino-carbonilo, aril-carbonilo, aralquil-carbonilo, hetero-aril-carbonilo, hetero-aralquil-carbonilo, tioalquilo, amino-alquilo, ciano-alquilo, arilo, y similares.

El grupo de sustitución puede estar él mismo sustituido.

El grupo sustituido sobre el grupo de sustitución puede ser carboxilo, halógeno; nitro, amino, ciano, hidroxilo, alquilo inferior, alcoxilo inferior, amino-carbonilo, -SR, tioamido, $-SO_3H$, $-SO_2R$ o cicloalquilo, en donde R es típicamente hidrógeno, hidroxilo o alquilo inferior.

Cuando el sustituyente sustituido incluye un grupo de cadena recta, la sustitución puede presentarse ya sea dentro de la cadena (por ejemplo, 2-hidroxi-propilo, 2-amino-butilo, y similares) o bien en el término de la cadena (por ejemplo, 2-hidroxi-etilo, 3-ciano-propilo, y similares). Los sustituyentes sustituidos pueden ser configuraciones de cadena recta, ramificada o cíclica de átomos de carbono o átomos heterogéneos covalentemente enlazados. Se entiende que las definiciones anteriores no pretenden incluir patrones de sustitución impermisibles (por ejemplo, metilo sustituido con cinco grupos flúor o un átomo de halógeno sustituido con otro átomo de halógeno). Estos patrones de sustitución impermisibles son bien conocidos por el experto.

También será evidente para los expertos en este campo que los compuestos de la invención, o sus estereoisómeros, así como las sales farmacéuticamente aceptables, ésteres, metabolitos, y pro-fármacos de cualquiera de los mismos, se pueden someter a tautomerización y, por consiguiente, pueden existir en diferentes formas tautoméricas, en donde un protón de un átomo de una molécula cambia hasta otro átomo, y

consecuentemente, se reconfiguran los enlaces químicos entre los átomos de las moléculas. Véase, por ejemplo, March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Cuarta Edición, John Wiley & Sons, páginas 69-74 (1992). Como se utiliza en la presente, el término "tautómero" se refiere a los compuestos producidos por el cambio de protones, y se debe entender que todas las formas tautoméricas, hasta donde puedan existir, se incluyen dentro de la invención.

Los compuestos de la invención, o sus tautómeros, así como las sales farmacéuticamente aceptables, ésteres, metabolitos, y pro-fármacos de cualquiera de los mismos, pueden comprender átomos de carbono asimétricamente sustituidos. Tales átomos de carbono asimétricamente sustituidos pueden dar como resultado que los compuestos de la invención existan en enantiómeros, diaestereómeros, y otras formas estereoisoméricas que se puedan definir en términos de estereoquímica absoluta, tales como en las formas (R) o (S). Como un resultado, todos los posibles isómeros, estereoisómeros individuales en sus formas ópticamente puras, mezclas de los mismos, mezclas racémicas (o "racematos"), mezclas de diaestereómeros, así como los diaestereómeros individuales de los compuestos de la invención, se incluyen en la presente invención. El término configuración "S" y "R", como se utiliza en la presente, es como lo define IUPAC 1974

RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure Appl. Chem. 45*: 13-30 (1976). Los términos α y ß se emplean para las posiciones de anillos de los compuestos cíclicos. El lado-α del plano de referencia es el lado sobre el cual queda el sustituyente preferido en la posición de numeración más baja. A los sustituyentes que queden sobre el lado opuesto del plano de referencia se les asigna el descriptor ß. Se debe observar que este uso difiere de aquél de los estereoprogenitores cíclicos, en donde "α" significa "debajo del plano" y denota la configuración absoluta. El término "configuración α y ß", como se utiliza en la presente, es como se define en CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) párrafo 203.

Como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a las sales de metales alcalinotérreos o de ácido no tóxicas de los compuestos de la fórmula I o II. Estas sales se pueden preparar *in situ* durante el aislamiento y purificación final de los compuestos de la fórmula I o II, o mediante la reacción por separado de las funciones de base o de ácido con un ácido o base orgánicos o inorgánicos adecuados, respectivamente. Las sales representativas incluyen, pero no se limitan a, las siguientes: acetato, adipato, alginato, citrato, aspartato, benzoato, bencen-sulfonato, bisulfato, butirato, canforato, canfor-sulfonato, digluconato, ciclopentan-propionato, dodecil-

sulfato, etan-sulfonato, glucoheptanoato, glicerofosfato, hemi-sulfato, heptanoato, hexanoato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxi-etan-sulfonato, lactato, maleato, metan-sulfonato, nicotinato, 2-naftalen-sulfonato, oxalato, pamoato, pectinato, persulfato, 3-fenil-propionato, picrato, pivalato, propionato, succinato, sulfato, tartrato, tiocianato, p-toluen-sulfonato, y undecanoato. También, los grupos que contienen nitrógeno básico se pueden cuaternizar con agentes tales como haluros de alquilo inferior, tales como cloruros, bromuros, y yoduros de metilo, etilo, propilo, y butilo; sulfatos de dialquilo, tales como sulfatos de dimetilo, dietilo, dibutilo, y diamilo; haluros de cadena larga, tales como cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo; haluros de aralquilo, tales como bromuros de bencilo y fenetilo, y otros. De esta manera, se obtienen productos solubles o dispersables en agua o en aceite.

Los ejemplos de los ácidos que se pueden emplear para formar las sales de adición de ácido farmacéuticamente aceptables incluyen los ácidos inorgánicos, tales como ácido clorhídrico, ácido sulfúrico y ácido fosfórico, y los ácidos orgánicos, tales como ácido oxálico, ácido maleico, ácido metan-sulfónico, ácido succínico y ácido cítrico. Las sales de adición básicas se pueden preparar *in situ* durante el aislamiento y purificación final de los compuestos de la fórmula (I), o por separado mediante la reacción de fracciones de ácido

carboxílico con una base adecuada, tal como el hidróxido, carbonato o bicarbonato de un catión de metal farmacéuticamente aceptable, o con amoníaco, o con una amina orgánica primaria, secundaria o terciaria. Las sales farmacéuticamente aceptables incluyen, pero no se limitan a, cationes basados en los metales alcalinos y alcalinotérreos, tales como las sales de sodio, litio, potasio, calcio, magnesio, aluminio, y similares, así como los cationes no tóxicos de amonio, amonio cuaternario, y amina, incluyendo, pero no limitándose a, amonio, tetrametil-amonio, tetraetil-amonio, metil-amina, dimetil-amina, trimetil-amina, trietil-amina, etil-amina, y similares. Otras aminas orgánicas representativas útiles para la formación de las sales de adición de base incluyen dietil-amina, etilen-diamina, etanolamina, dietanolamina, piperazina y similares.

Como se utiliza en la presente, el término "éster farmacéuticamente aceptable" se refiere a los ésteres que se hidrolizan *in vivo* e incluyen aquéllos que se descomponen fácilmente en el cuerpo humano para dejar el compuesto progenitor o una sal del mismo. Los grupos éster adecuados incluyen, por ejemplo, aquéllos derivados a partir de ácidos carboxílicos alifáticos farmacéuticamente aceptables, en particular los ácidos alcanoico, alquenoico, cicloalcanoico, y alcanodioico, en donde cada fracción de alquilo o alquenilo convenientemente no tiene más de 6 átomos de carbono. Los

ejemplos de los ésteres particulares incluyen formatos, acetatos, propionatos, butiratos, acrilatos, y etil-succinatos.

El término "pro-fármacos farmacéuticamente aceptables", como se utiliza en la presente, se refiere a los pro-fármacos de los compuestos de la presente invención que, dentro del alcance de un buen juicio médico, son adecuados para utilizarse en contacto con los tejidos de los seres humanos y de animales inferiores sin una indebida toxicidad, irritación, respuesta alérgica, y similares, de una manera conmensurada con una proporción razonable de beneficio/riesgo, y efectivos para su uso pretendido, así como las formas zwiteriónicas, donde sea posible, de los compuestos de la invención. El término "pro-fármaco" se refiere a los compuestos que se transforman rápidamente *in vivo* para proporcionar el compuesto progenitor de la fórmula anterior, por ejemplo mediante hidrólisis en la sangre. Se proporciona una discusión completa en T. Higuchi y V. Stella, Pro-drugs as Novel Delivery Systems, Volumen 14 de la serie A.C.S. Symposium Series, y en Edward B. Roche, Editor, Bioreversible Vehicles in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, ambos de los cuales se incorporan a la presente como referencia.

Cualquier fórmula dada en la presente también pretende representar las formas no marcadas así como las formas isotópicamente marcadas de los compuestos. Los compuestos

isotópicamente marcados tienen las estructuras ilustradas por las fórmulas dadas en la presente, excepto que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa seleccionados. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectivamente. La invención incluye diferentes compuestos isotópicamente marcados como se definen en la presente, por ejemplo aquéllos en donde hay isótopos radioactivos presentes, tales como ^{3}H, ^{13}C, y ^{14}C. Estos compuestos isotópicamente marcados son útiles en los estudios metabólicos (con ^{14}C), en los estudios de cinética de reacción (con, por ejemplo ^{2}H ó ^{3}H), en las técnicas de detección o de formación de imágenes, tales como la tomografía por emisión de positrones (PET) o la tomografía computarizada con emisión de un solo fotón (SPECT), incluyendo los ensayos de distribución del fármaco o del sustrato en el tejido, o en el tratamiento radioactivo de los pacientes. En particular, puede ser particularmente deseable un ^{18}F o un compuesto marcado para los estudios de PET o SPECT. Los compuestos isotópicamente marcados de esta invención y los pro-fármacos de los mismos se pueden preparar en términos generales llevando a cabo los procedimientos que se dan a conocer en los esquemas o en los Ejemplos y

preparaciones que se describen más adelante, mediante la utilización de un reactivo isotópicamente marcado fácilmente disponible para sustituir a un reactivo no isotópicamente marcado.

Además, la sustitución con isótopos más pesados, en particular deuterio (es decir, ^{2}H o D), puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo un aumento de la vida media *in vivo,* o requerimientos de dosificación reducida, o una mejora en el índice terapéutico. Se entiende que el deuterio en este contexto se considera como un sustituyente de un compuesto de la fórmula (I). La concentración de este isótopo más pesado, específicamente deuterio, se puede definir por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico", como se utiliza en la presente, significa la proporción entre la abundancia isotópica y la abundancia natural de un isótopo especificado. Si un sustituyente en un compuesto de esta invención es denotado como deuterio, este compuesto tiene un factor de enriquecimiento isotópico para cada átomo de deuterio designado de cuando menos 3,500 (52.5 por ciento de incorporación de deuterio en cada átomo de deuterio designado), cuando menos 4,000 (60 por ciento de incorporación de deuterio), cuando menos 4,500 (67.5 por ciento de incorporación de deuterio), cuando menos 5,000 (75

por ciento de incorporación de deuterio), cuando menos 5,500 (82.5 por ciento de incorporación de deuterio), cuando menos 6,000 (90 por ciento de incorporación de deuterio), cuando menos 6,333.3 (95 por ciento de incorporación de deuterio), cuando menos 6,466.7 (97 por ciento de incorporación de deuterio), cuando menos 6,600 (99 por ciento de incorporación de deuterio), o cuando menos 6,633.3 (99.5 por ciento de incorporación de deuterio).

Los compuestos isotópicamente marcados de la fórmula (I) se pueden preparar en términos generales mediante técnicas convencionales conocidas para los expertos en este campo o mediante procesos análogos a aquéllos descritos en los Ejemplos y preparaciones acompañantes, utilizando un reactivo isotópicamente marcado apropiado en lugar del reactivo no marcado anteriormente empleado.

Será evidente para los expertos en este campo que los compuestos de la invención, o sus tautómeros, pro-fármacos y estereoisómeros, así como las sales farmacéuticamente aceptables, ésteres y pro-fármacos de cualquiera de los mismos, se pueden procesar *in vivo* a través del metabolismo en un cuerpo humano o animal o en una célula para producir metabolitos. El término "metabolito", como se utiliza en la presente, se refiere a la fórmula de cualquier derivado producido en un sujeto después de la administración de un compuesto progenitor. Los derivados se pueden producir a

partir del compuesto progenitor mediante diferentes transformaciones bioquímicas en el sujeto, tales como, por ejemplo, oxidación, reducción, hidrólisis, o conjugación, e incluyen, por ejemplo, óxidos y derivados desmetilados. Los metabolitos de un compuesto de la invención se pueden identificar empleando las técnicas de rutina conocidas en la materia. Véase, por ejemplo, Bertolini, G. y colaboradores, *J. Med. Chem. 40*: 2011-2016 (1997); Shan, D. y colaboradores, *J. Pharm. Sci. 86*(7): 765-767; Bagshawe K., *Drug Dev. Res. 34*: 220-230 (1995); Bodor, N., *Advances in Drug Res. 13*: 224-331 (1984); Bundgaard, H., *Design of Pro-drugs* (Elsevier Press 1985); y Larsen, I. K., *Design and Application of Pro-drugs, Drug Design and Development* (Krogsgaard-Larsen y colaboradores, editores, Harwood Academic Publishers, 1991). Se debe entender que los compuestos químicos individuales que sean metabolitos de los compuestos de la fórmula I, de la fórmula II, o sus tautómeros, pro-fármacos y estereoisómeros, así como las sales farmacéuticamente aceptables, ésteres y pro-fármacos de cualquiera de los mismos, se incluyen dentro de la invención.

El término "cáncer" se refiere las enfermedades de cáncer que se puedan tratar benéficamente mediante la inhibición de la cinasa Pim, incluyendo, por ejemplo, cánceres sólidos, tales como carcinomas (por ejemplo, de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon), melanomas,

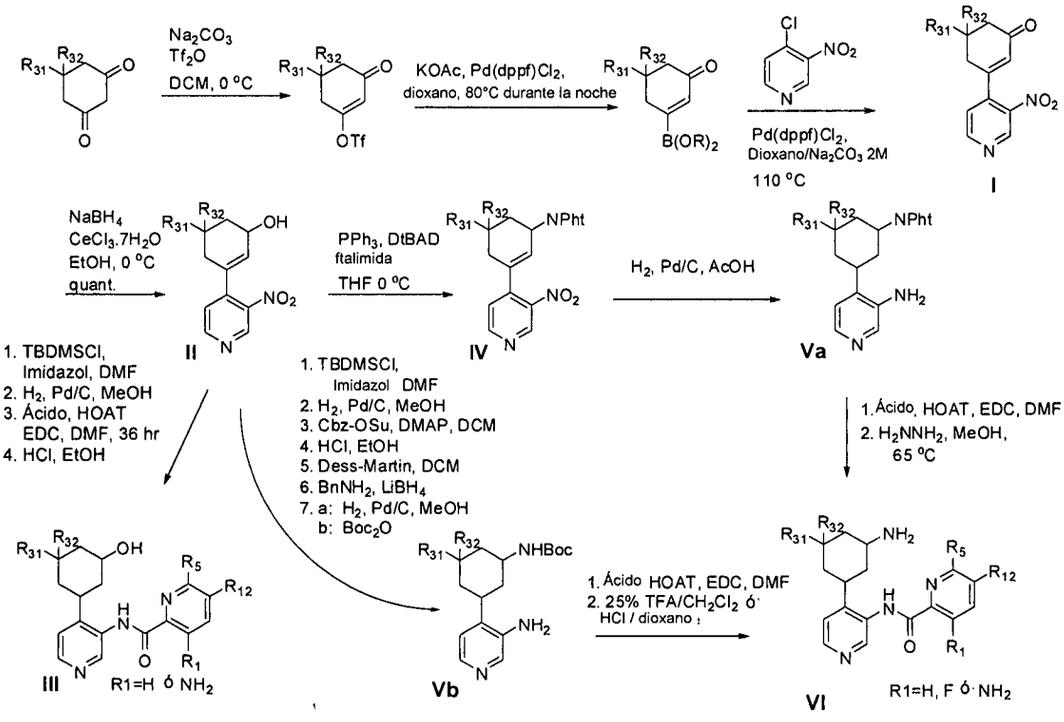
trastornos mieloides (por ejemplo, leucemia mieloide, mieloma múltiple, y eritroleucemia), adenomas (por ejemplo, adenoma de colon velloso), y sarcomas (por ejemplo, osteosarcoma).

METODOS SINTETICOS

Los compuestos de la invención se pueden obtener a través de los procedimientos conocidos por el experto en este campo. Por ejemplo, como se muestra en el esquema 1, las ciclohexanodionas se pueden convertir por medio de monotriflatos hasta los ésteres de boronato de ciclohexenona correspondientes, los cuales pueden someterse a formación de enlace de carbono mediada por paladio con 4-cloro-3-nitro-piridina, para proporcionar las ciclohexenonas sustituidas por nitro-piridina I. La reducción de la funcionalidad de enona puede proporcionar un ciclohexenol II, el cual, después de la protección de alcohol, la reducción de nitro y alqueno, el acoplamiento de amida, y la desprotección, puede proporcionar las ciclohexanol-amidas III. El ciclohexenol II también puede sufrir reacción de Mitsunobu con ftalimida para proporcionar un amino-ciclohexeno protegido IV. En seguida de la reducción de nitro y alqueno, la amino-ciclohexil-piridil-anilina protegida por ftalimida Va puede someterse a acoplamiento de amida y desprotección, para proporcionar las amino-ciclohexan-amidas VI. La amino-ciclohexan-piridil-anilina protegida por Boc Vb correspondiente se puede preparar a partir del ciclohexenol II de la siguiente manera: protección de alcohol, reducción de

alqueno y nitro, protección con Cbz de piridil-amina, desprotección de silil-éter, oxidación Dess-Martin hasta la ciclohexanona, aminación reductiva con bencil-amina, desprotección de Cbz y Bn, y protección con Boc de amina alifática primaria. En los productos de amida III y VI, si R_2 es halógeno o triflato, las amidas III y VI se pueden modificar adicionalmente mediante modificaciones convencionales para introducir los arilos, alquilos y heteroarilos sustituidos en R_2. Por ejemplo, si R_2 es Br, mediante la reacción con ácidos borónicos o reactivos organometálicos, o mediante la conversión hasta el éster de boronato correspondiente y la reacción con haluros o triflatos de arilo/heteroarilo, son posibles una variedad de modificaciones de R_2.

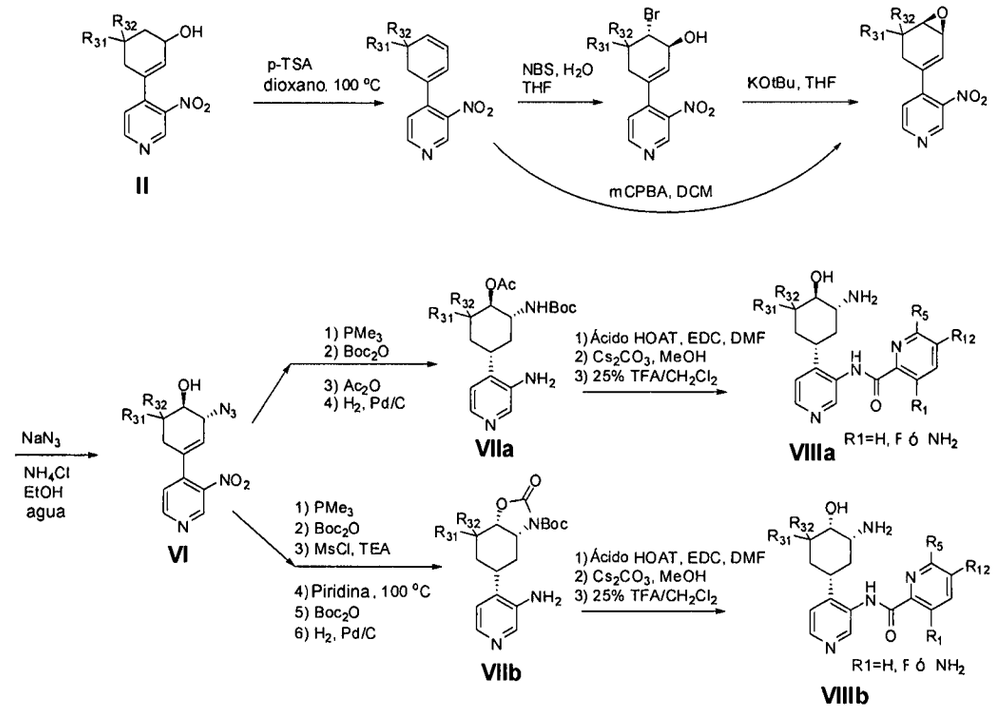
Esquema 1



De una manera alternativa, como se muestra en el esquema 2, el ciclohexenol II se puede deshidratar, proporcionando un ciclohexadieno, el cual, después de la epoxidación (por medio de la formación de bromohidrina y la eliminación de HBr, o a partir del mCPBA directamente), y la abertura del epóxido de azida, proporciona el ciclohexenil-azido-alcohol VI. El ciclohexenil-azido-alcohol VI se puede convertir hasta la amino- hidroxil-anilina trans-protegida VIIa mediante la reducción de azida, la protección de alcohol, y la reducción de alqueno y nitro. De una manera alternativa, el ciclohexenil-azido-alcohol VI se puede convertir hasta la cis-amino-hidroxil-anilina protegida VIIb mediante reducción de azida y protección de Boc, mesilación de alcohol, y ciclación intramolecular hasta el cis-carbamato cíclico, seguida por protección de Boc y reducción de alqueno y nitro. Las ciclohexil-piridilo-anilinas VIIa y VIIb resultantes se pueden convertir hasta las piridin-amidas VIIIa y VIIIb correspondientes mediante acoplamiento de amida, disociación de acetato o carbamato cíclico, y desprotección de Boc. Si R_2 es halógeno o triflato, las amidas VIIIa y VIIIb se pueden modificar adicionalmente mediante modificaciones convencionales para introducir los arilos, alquilos y heteroarilos sustituidos en R_2, después de la formación del enlace de amida y antes de la desprotección completa. Por ejemplo, si R_2 es Br, mediante la reacción con ácidos borónicos o reactivos organometálicos, o

mediante la conversión hasta el éster de boronato correspondiente y la reacción con haluros o triflatos de arilo/heteroarilo, son posibles una variedad de modificaciones de R_2.

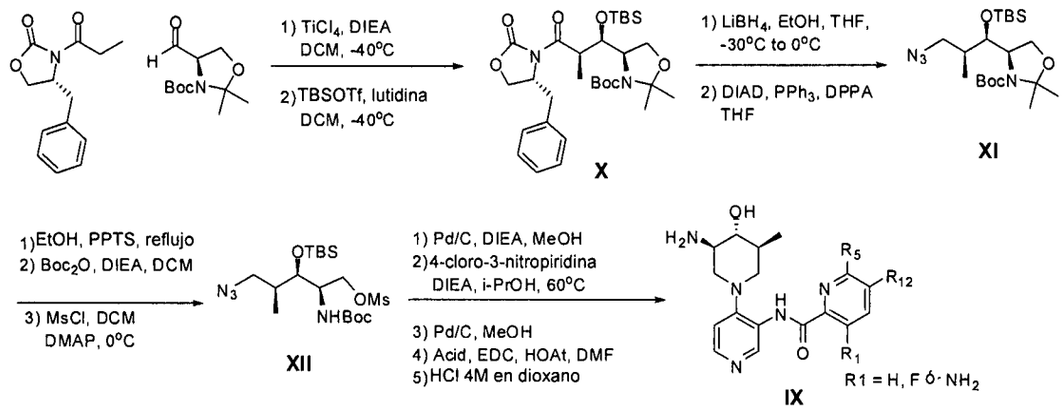
Esquema 2



De una manera alternativa, como se muestra en el esquema 3, las 5-alquil-4-hidroxi-3-amino-piperidinas trisustituidas se pueden preparar y modificar para proporcionar las 5-alquil-4-hidroxi-3-amino-piperidinil-piridin-amidas trisustituidas IX como sigue. La reacción de aldehído de Garner con (R)-4-bencil-3-propionil-oxazolidin-2-ona, seguida por protección con TBS del alcohol resultante, proporciona el compuesto X. La reducción de la oxazolidinona, seguida por la introducción del grupo azida, proporciona el Intermediario XI.

La desprotección bajo condiciones ácidas revela el amino-alcohol correspondiente, el cual, después de la protección con el grupo Boc, seguida por mesilación del alcohol primario, proporciona el Intermediario XII. La reducción de la azida proporciona la formación de la piperidina, la cual subsiguientemente se hace reaccionar con la 4-cloro-3-nitro-piridina, se reduce hasta la amina, se acopla con el ácido carboxílico correspondiente, y se desprotege para proporcionar las 5-metil-4-hidroxi-3-amino-piperidinil-piridin-amidas tri-sustituidas IX. Si R_1 es halógeno o triflato, la amida IX se puede modificar adicionalmente mediante modificaciones convencionales para introducir los arilos, alquilos y heteroarilos sustituidos en R_1 después de la formación del enlace de amida y antes de la desprotección completa. Por ejemplo, si R_1 es Br, mediante la reacción con ácidos borónicos o con reactivos organometálicos, o la conversión hasta el éster de boronato correspondiente y la reacción con los haluros o triflatos de arilo/heteroarilo, son posibles una variedad de modificaciones de R_1.

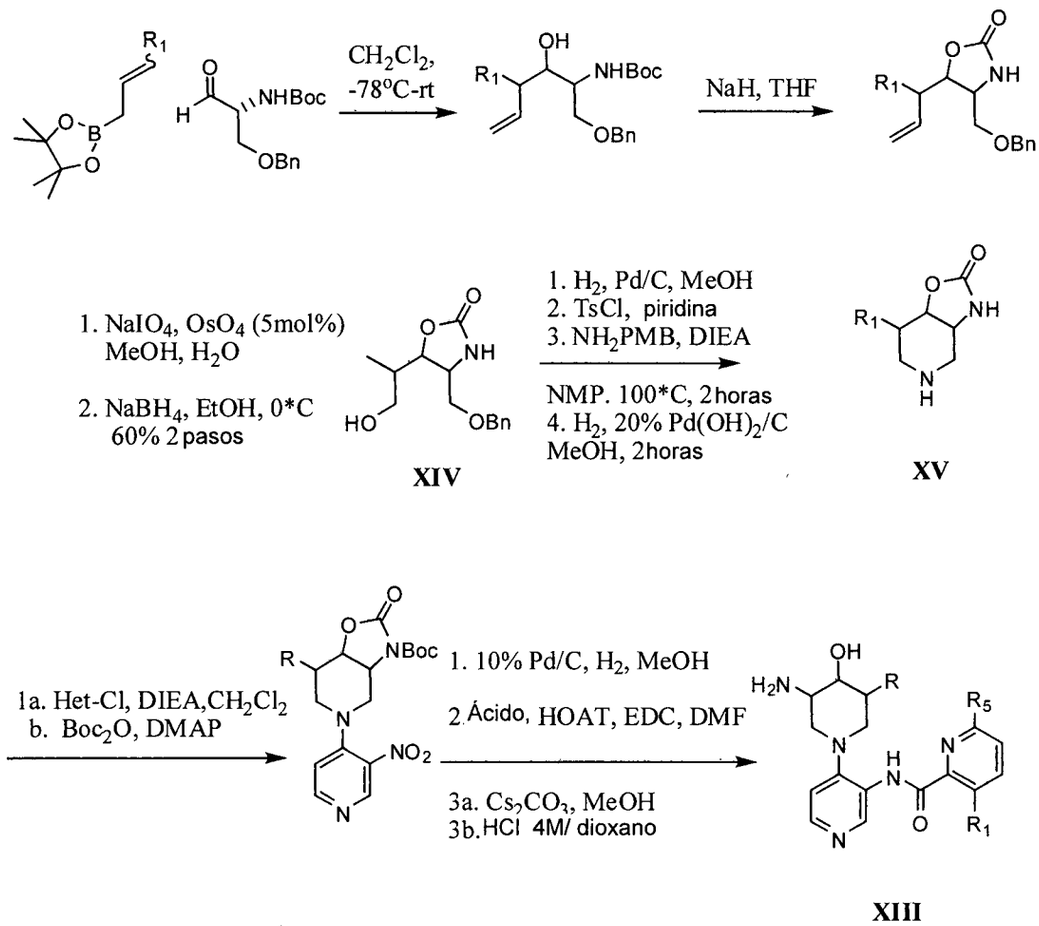
Esquema 3



De una manera alternativa, como se muestra en el esquema 4, las 5-metil-4-hidroxi-3-amino-piperidinas tri-sustituidas también se pueden preparar y modificar para proporcionar las 5-metil-4-hidroxi-3-amino-piperidinil-amidas tri-sustituidas XIII como sigue. La reacción de los ésteres de boronato de crotilo con el aldehído SerOBn, seguida por la formación del carbamato cíclico, la disociación oxidativa de alqueno, y la reducción, proporcionan el compuesto de hidroxilo XIV. La desprotección de bencilo, seguida por bis-tosilación, y la reacción con p-metoxi-bencil-amina, y la desprotección de amina, proporcionan la piperidina XV. La reacción de la piperidina sustituida XV con arenos o heteroarenos sustituidos por halógeno-nitro, seguida por protección de carbamato, reducción de nitro, acoplamiento de amida, abertura del carbamato cíclico, y desprotección, proporcionan las 5-metil-4-hidroxi-3-amino-piperidinil-amidas tri-sustituidas XIII. Si R_3 es halógeno o triflato, la amida XV se puede modificar

adicionalmente mediante modificaciones convencionales para introducir los arilos, alquilos y heteroarilos sustituidos en R_3. Por ejemplo, si R_3 es Br, mediante la reacción con ácidos borónicos o reactivos organometálicos, o la conversión hasta el éster de boronato correspondiente, y la reacción con haluros o triflatos de arilo/heteroarilo, son posibles una variedad de modificaciones de R_3.

Esquema 4



Los compuestos de la invención son útiles *in vitro* y/o *in vivo* en la inhibición del crecimiento de las células de cáncer.

Los compuestos se pueden utilizar solos o en composiciones junto con un vehículo o excipiente farmacéuticamente aceptable. Los vehículos o excipientes farmacéuticamente aceptables adecuados incluyen, por ejemplo, agentes de procesamiento y modificadores y potenciadores del suministro de fármacos, tales como, por ejemplo, fosfato de calcio, estearato de magnesio, talco, monosacáridos, disacáridos, almidón, gelatina, celulosa, metil-celulosa, carboxi-metil-celulosa de sodio, dextrosa, hidroxi-propil-ß-ciclodextrina, polivinil-pirrolidinona, ceras de bajo punto de fusión, resinas de intercambio de iones, y similares, así como combinaciones de cualesquiera dos o más de los mismos. Otros excipientes farmacéuticamente aceptables adecuados se describen en "Remington's Pharmaceutical Sciences," Mack Pub. Co., Nueva Jersey (1991), incorporado a la presente como referencia.

Las cantidades efectivas de los compuestos de la invención en términos generales incluyen cualquier cantidad suficiente para inhibir detectablemente la actividad de Pim mediante cualquiera de los ensayos descritos en la presente, mediante otros ensayos de la actividad de cinasa Pim conocidos por aquellos que tengan una experiencia ordinaria en este campo, o mediante la detección de una inhibición o alivio de los síntomas de cáncer. La cantidad de ingrediente activo que se puede combinar con los materiales portadores para producir una sola forma de dosificación variará dependiendo

del huésped tratado y del modo particular de administración. Se entenderá, sin embargo, que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la edad, el peso corporal, la salud general, el sexo, la dieta, el tiempo de administración, la vía de administración, el índice de excreción, la combinación de fármacos, y la gravedad de la enfermedad particular que se esté sometiendo a terapia. La cantidad terapéuticamente efectiva para una situación dada puede ser determinada fácilmente mediante experimentación de rutina, y está dentro de la experiencia y juicio del clínico ordinario.

Para los propósitos de la presente invención, una dosis terapéuticamente efectiva, en términos generales, será una dosis diaria total administrada a un huésped en una sola dosis o en dosis divididas que pueden ser en cantidades, por ejemplo, de 0.001 a 1,000 miligramos/kilogramo de peso corporal al día, y más preferiblemente de 1.0 a 30 miligramos/kilogramo de peso corporal al día. Las composiciones unitarias de dosificación pueden contener las cantidades de los submúltiplos de las mismas para formar la dosis diaria.

Los compuestos de la presente invención se pueden administrar oralmente, parenteralmente, sublingualmente, mediante aerosolización o rocío para inhalación, rectalmente, o

tópicamente, en formulaciones unitarias de dosificación que contengan los portadores, adyuvantes, y vehículos no tóxicos farmacéuticamente aceptables que se deseen. La administración tópica también puede involucrar el uso de administración transdérmica, tal como parches transdérmicos o dispositivos de ionoforesis. El término "parenteral", como se utiliza en la presente, incluye inyecciones subcutáneas, inyección intravenosa, intramuscular, intraesternal, o técnicas de infusión.

Las preparaciones inyectables, por ejemplo, las suspensiones acuosas u oleaginosas inyectables estériles, se pueden formular de acuerdo con la técnica conocida, utilizando agentes de dispersión o humectantes adecuados, y agentes de suspensión. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-propanodiol. Entre los vehículos y solventes aceptables que se pueden emplear están agua, solución de Ringer, y solución isotónica de cloruro de sodio. En adición, convencionalmente se emplean aceites fijos estériles como un solvente o medio de suspensión. Para este propósito, se puede emplear cualquier aceite fijo blando, incluyendo mono- o di-glicéridos sintéticos. En adición, los ácidos grasos, tales como ácido oleico, encuentran uso en la preparación de inyectables.

Los supositorios la administración rectal del fármaco se pueden preparar mediante la mezcla del fármaco con un excipiente no irritante adecuado, tal como manteca de cacao y polietilenglicoles, los cuales son sólidos a la temperaturas ordinarias pero líquidos a la temperatura rectal, y, por consiguiente, se funden en el recto y liberan el fármaco.

Las formas de dosificación sólidas para su administración oral pueden incluir cápsulas, tabletas, píldoras, polvos, y gránulos. En estas formas de dosificación sólidas, el compuesto activo se puede mezclar con cuando menos un diluyente inerte, tal como sacarosa, lactosa, o almidón. Estas formas de dosificación también pueden comprender, como es la práctica normal, sustancias adicionales diferentes de los diluyentes inertes, por ejemplo, agentes lubricantes tales como estearato de magnesio. En el caso de las cápsulas, tabletas, y píldoras, las formas de dosificación también pueden comprender agentes reguladores del pH. Las tabletas y píldoras se pueden preparar adicionalmente con recubrimientos entéricos.

Las formas de dosificación líquidas para administración oral pueden incluir emulsiones, soluciones, suspensiones, jarabes, y elíxires farmacéuticamente aceptables conteniendo los diluyentes inertes comúnmente utilizados en la técnica, tales como agua. Estas composiciones también pueden comprender adyuvantes, tales como agentes humectantes,

agentes emulsionantes y de suspensión, ciclodextrinas, y agentes edulcorantes, saborizantes, y perfumantes.

Los compuestos de la presente invención también se pueden administrar en la forma de liposomas. Como se conoce en este campo, los liposomas se derivan generalmente a partir de fosfolípidos u otras sustancias de lípido. Los liposomas se forman mediante cristales líquidos hidratados mono- o multi-lamelares que se dispersan en un medio acuoso. Se puede utilizar cualquier lípido no tóxico, fisiológicamente aceptable y metabolizable. Las presentes composiciones en forma de liposomas pueden contener, en adición a un compuesto de la presente invención, estabilizantes, conservadores, excipientes, y similares. Los lípidos preferidos son los fosfolípidos y las fosfatidil-colinas (lecitinas), tanto naturales como sintéticos. Los métodos para formar liposomas son conocidos en la materia. Véase, por ejemplo, Prescott, Editor, *Methods in Cell Biology*, Volumen XIV, Academic Press, Nueva York, N.Y., páginas 33 y siguientes (1976).

Aunque los compuestos de la invención se pueden administrar como el único agente farmacéutico activo, también se pueden utilizar en combinación con uno o más agentes diferentes utilizados en el tratamiento de cáncer. Los compuestos de la presente invención son también útiles en combinación con los agentes terapéuticos y agentes contra cáncer conocidos, y las combinaciones de los compuestos

actualmente dados a conocer, con otros agentes contra el cáncer o agentes quimioterapéuticos están dentro del alcance de la invención. Los ejemplos de estos agentes se pueden encontrar en *Cancer Principles and Practice of Oncology*, V. T. Devita y S. Hellman (Editores), 6ª Edición (Febrero 15, 2001), Lippincott Williams & Wilkins Publishers. Una persona de una experiencia ordinaria en este campo sería capaz de discernir cuáles combinaciones de agentes serían útiles basándose en las características particulares de los fármacos y del cáncer involucrado. Estos agentes contra el cáncer incluyen, pero no se limitan a, los siguientes: moduladores de receptores de estrógeno, moduladores de receptores de andrógeno, moduladores de receptores de retinoides, agentes citotóxicos/citostáticos, agentes anti-proliferativos, inhibidores de prenil-transferasa de proteína, inhibidores de HMG-CoA-reductasas y otros inhibidores de angiogénesis, inhibidores de la señalización de proliferación y sobrevivencia celular, agentes inductores de apoptosis, y agentes que interfieren con los puntos de verificación del ciclo celular. Los compuestos de la invención son también útiles cuando se co-administran con terapia de radiación.

Por consiguiente, en una modalidad de la invención, los compuestos de la invención también se utilizan en combinación con los agentes contra el cáncer conocidos, incluyendo, por ejemplo, moduladores de receptores de estrógeno, moduladores

de receptores de andrógeno, moduladores de receptores de retinoides, agentes citotóxicos, agentes anti-proliferativos, inhibidores de la prenil-transferasa de proteína, inhibidores de HMG-CoA-reductasas, inhibidores de proteasa de VIH, inhibidores de transcriptasa inversa, y otros inhibidores de angiogénesis.

En ciertas modalidades actualmente preferidas de la invención, los agentes representativos útiles en combinación con los compuestos de la invención para el tratamiento de cáncer incluyen, por ejemplo, irinotecano, topotecano, gemcitabina, 5-fluoro-uracilo, leucovorina, carboplatina, cisplatina, taxanos, tezacitabina, ciclofosfamida, alcaloides vinca, imatinib (Gleevec), antraciclinas, rituximab, trastuzumab, así como otros agentes quimioterapéuticos para el cáncer.

Los compuestos anteriores que se van a emplear en combinación con los compuestos de la invención se utilizarán en las cantidades terapéuticas, como se indican en *Physicians' Desk Reference* (PDR) 47ª Edición (1993), el cual se incorpora a la presente como referencia, o las cantidades terapéuticamente útiles que sean conocidas por una persona de una experiencia ordinaria en este campo.

Los compuestos de la invención y los otros agentes contra el cáncer se pueden administrar en la dosificación clínica máxima recomendada o en dosis más bajas. Los niveles de dosificación de los compuestos activos en las composiciones de

la invención se pueden variar para obtener una respuesta terapéutica deseada, dependiendo de la vía de administración, de la gravedad de la enfermedad, y de la respuesta del paciente. La combinación se puede administrar como composiciones separadas o como una sola forma de dosificación que contenga ambos agentes. Cuando se administran como una combinación, los agentes terapéuticos se pueden formular como composiciones separadas, las cuales se dan al mismo tiempo o en diferentes tiempos, o los agentes terapéuticos se pueden dar como una sola composición.

En una modalidad, la invención proporciona un método para inhibir Pim1, Pim2 o Pim3 en un sujeto humano o animal. El método incluye administrar una cantidad efectiva de un compuesto, o una sal farmacéuticamente aceptable del mismo, de cualquiera de las modalidades de los compuestos de la fórmula I o II, a un sujeto que lo necesite.

La presente invención se entenderá más fácilmente haciendo referencia a los siguientes ejemplos, los cuales se proporcionan a manera de ilustración, y no se pretende que sean limitantes de la presente invención.

EJEMPLOS

Haciendo referencia a los siguientes Ejemplos, los compuestos de las modalidades preferidas se sintetizaron empleando los métodos descritos en la presente, u otros métodos, los cuales son conocidos en la materia.

Los compuestos y/o intermediarios se caracterizaron mediante cromatografía de líquidos de alto rendimiento (HPLC) utilizando un sistema de cromatografía Waters Millenium con un Módulo de Separación 2695 (Milford, MA). Las columnas analíticas fueron Fenomenex La C18 - 5 micras, 4.6 x 50 milímetros, de fase inversa, de Alltech (Deerfield, IL). Se utilizó una elución en gradiente (flujo de 2.5 mililitros/minuto), típicamente empezando con 5 por ciento de acetonitrilo/95 por ciento de agua y progresando hasta el 100 por ciento de acetonitrilo durante un período de 10 minutos. Todos los solventes contuvieron ácido trifluoro-acético al 0.1 por ciento (TFA). Los compuestos se detectaron mediante absorción de luz ultravioleta (UV) a cualquiera de 220 ó 254 nanómetros. Los solventes de HPLC fueron de Burdick and Jackson (Muskegan, MI), o de Fisher Scientific (Pittsburgh, PA).

En algunos casos, la pureza se evaluó mediante cromatografía de capa delgada (TLC) utilizando placas de gel de sílice con respaldo de vidrio o de plástico, tales como, por ejemplo, hojas flexibles de gel de sílice Baker-Flex 1B2-F. Los resultados de la TLC se detectaron con facilidad visualmente bajo luz ultravioleta, o empleando vapor de yodo bien conocido y otras diferentes técnicas de teñido.

El análisis espectrométrico de masas se llevó a cabo en uno de tres instrumentos de LCM: un Sistema Waters (Alliance

HT HPLC, y un espectrómetro de masas Micromass ZQ; Columna: Eclipse XDB-C18, 2.1 x 50 milímetros; gradiente: del 5 al 95 por ciento (o del 35 al 95 por ciento, o del 65 al 95 por ciento o del 95 al 95 por ciento) de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento durante un período de 4 minutos; velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 200 a 1,500; voltaje del cono de 20 V; temperatura de la columna de 40°C), otro Sistema Waters (Sistema ACQUITY UPLC y un Sistema ZQ 2000; Columna: ACQUITY UPLC HSS-C18, 1.8 micras, 2.1 x 50 milímetros; gradiente: del 5 al 95 por ciento (o del 35 al 95 por ciento, o del 65 al 95 por ciento o del 95 al 95 por ciento) de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento durante un período de 1.3 minutos; velocidad de flujo de 1.2 mililitros/minuto; intervalo de peso molecular de 150 a 850; voltaje del cono de 20 V; temperatura de la columna de 50°C), o un Sistema Hewlett Packard (Serie 1100 HPLC; Columna: Eclipse XDB-C18, 2.1 x 50 milímetros; gradiente: del 5 al 95 por ciento de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento durante un período de 4 minutos; velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 150 a 850; voltaje del cono de 50 V; temperatura de la columna de 30°C). Todas las masas se reportaron como aquéllas de los iones progenitores protonados.

El análisis de resonancia magnética nuclear (RMN) se

llevó a cabo sobre algunos de los compuestos con un Varian 400 MHz RMN (Palo Alto, CA). La referencia espectral fue cualquiera de TMS el cambio químico conocido del solvente.

Las separaciones de preparación se llevan a cabo utilizando un sistema de cromatografía Flash 40 y KP-Sil, 60A (Biotage, Charlottesville, VA), o mediante cromatografía por evaporación instantánea en columna utilizando un material de empaque de gel de sílice (malla 230-400), o mediante HPLC utilizando un Manejador de Muestras Waters 2767, columna de fase inversa C-18, 30 X 50 milímetros, flujo: 75 mililitros/minuto. Los solventes típicos empleados para el sistema Flash 40 Biotage y para la cromatografía por evaporación instantánea en columna son dicloro-metano, metanol, acetato de etilo, hexano, acetona, amoníaco acuoso (o hidróxido de amonio), y trietil-amina. Los solventes típicos empleados para la HPLC de fase inversa son concentraciones variables de acetonitrilo y agua con ácido trifluoro-acético al 0.1 por ciento.

Se debe entender que los compuestos orgánicos de acuerdo con las modalidades preferidas pueden exhibir el fenómeno de tautomerismo. Debido a que las estructuras químicas dentro de esta memoria descriptiva pueden representar solamente una de las posibles formas tautoméricas, se debe entender que las modalidades preferidas abarcan

cualquier forma tautomérica de la estructura dibujada.

Se entiende que la invención no está limitada a las modalidades estipuladas en la presente para ilustración, sino que abarca todas las formas de las mismas que entren en el alcance de la divulgación anterior.

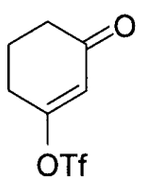
En los Ejemplos que se encuentran más adelante, así como a través de toda la solicitud, las siguientes abreviaturas tienen los siguientes significados. Si no se definen, los términos tienen sus significados generalmente aceptados.

ABREVIATURAS

DAST	Trifluoruro de (dietil-amino)-azufre
DCM	Dicloro-metano
DIEA	Di-isopropil-etil-amina
DMA	Dimetil-acetamida
DMAP	4-dimetil-amino-piridina
DME	1,2-dimetoxi-etano
DMF	*N,N*-dimetil-formamida
DPPF	1,1'-bis-(difenil-fosfino)-ferroceno
EDC	Clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida
EtOAc	Acetato de etilo
EtOH	Etanol
HOAT	Hidroxi-aza-benzotriazol
K_2CO_3	Carbonato de potasio
MeCN	Acetonitrilo

$MgSO_4$	Sulfato de magnesio
MeOH	Metanol
Na_2CO_3	Carbonato de sodio
NaCl	Cloruro de sodio
$NaHCO_3$	Bicarbonato de sodio
NBS	*N*-bromo-succinimida
NMP	*N*-metil-2-pirrolidona
$Pd_2(dba)_3$	Tris-(dibenciliden-acetona)-dipaladio(0)
$Pd(PPh_3)_4$	Tetraquis-(trifenil-fosfina)-paladio(0)
$Pd(dppf)Cl_2$-DCM	Aducto de dicloro-(1,2-bis-(difenil-fosfino)-etan)-paladio(II) / dicloro-metano
RT o rt	Temperatura ambiente
TBDMSCl	Cloruro de ter-butil-dimetil-sililo
TEA	Trietil-amina
THF	Tetrahidrofurano

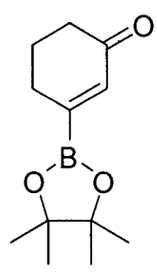
Síntesis de trifluoro-metan-sulfonato de 3-oxociclohex-1-enilo



A una solución de ciclohexano-1,3-diona (1 equivalente) en dicloro-metano (0.4M), se le agregó Na_2CO_3 (1.0

equivalentes) y se enfrió a 0°C. Se le agregó Tf_2O (1.0 equivalentes) en dicloro-metano (5M) por goteo durante 1 hora a temperatura ambiente bajo una atmósfera de nitrógeno. Después de la adición, la reacción se agitó durante 2 horas (solución color rojo oscuro). La solución se filtró, y al filtrado se le agregó (cuidadosamente) $NaHCO_3$ saturado, entonces se extrajeron los orgánicos, se secaron con salmuera, luego Na_2SO_4, y se concentraron. El crudo se utilizó para el siguiente paso sin mayor purificación. Se obtuvo el trifluoro-metan-sulfonato de 3-oxo-ciclohex-1-enilo en un 67 por ciento de rendimiento. El triflato se descompone debido al almacenamiento y debería utilizarse inmediatamente para la siguiente reacción. LC/MS=244.9/286.0 (M+H y M+CH_3CN); Rt = 0.88 minutos.

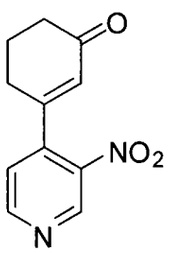
Síntesis de 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona



A una solución del trifluoro-metan-sulfonato de 3-oxociclohex-1-enilo (1.0 equivalentes) en dioxano desgasificado (0.3M), se le agregaron bis-(pinacolato)-diboro (2.0

equivalentes), KOAc (3.0 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes). La reacción se calentó a 80°C durante 2 horas, y entonces se filtró. La solución de dioxano se utilizó para el siguiente paso sin mayor purificación. LC/MS = 140.9 (M+H de ácido borónico).

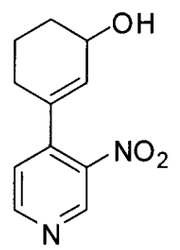
Síntesis de 3-(3-nitro-piridin-4-il)-ciclohex-2-enona



A una solución de la 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona (1.0 equivalentes) en dioxano desgasificado y Na_2CO_3 2M, se le agregaron 4-cloro-3-nitro-piridina (1.2 equivalentes) y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes). La reacción se calentó en un baño de aceite hasta 110°C durante 2 horas. Se enfrió a temperatura ambiente, luego se diluyó con EtOAc, y se le agregaron varias emulsiones de H_2O – solución oscura. Se filtró para dar la liberación de los sólidos, entonces se extrajo la fase orgánica, se secó con Na_2SO_4, y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para proporcionar la 3-(3-nitro-piridin-4-il)-ciclohex-2-enona (55 por ciento, 2 pasos).

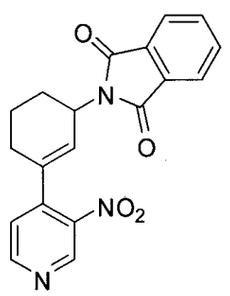
LC/MS = 219 (M+H), LC = 2.294 minutos.

Síntesis de 3-(3-nitro-piridin-4-il)-ciclohex-2-enol



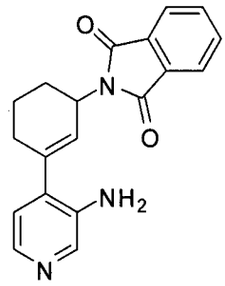
A una solución de la 3-(3-nitro-piridin-4-il)-ciclohex-2-enona (1.0 equivalentes), se le agregó EtOH (0.2 M), y $CeCl_3$-$7H_2O$ (1.3 equivalentes). La reacción se enfrió a 0°C, y entonces se le agregó en porciones $NaBH_4$ (1.3 equivalentes). Se agitó durante 2 horas a 0°C, entonces se apagó mediante la adición de agua, se concentró para remover el EtOH, se agregó EtOAc, se extrajeron los orgánicos, se secaron con salmuera, luego Na_2SO_4, y se concentraron, para proporcionar el 3-(3-nitro-piridin-4-il)-ciclohex-2-enol (99 por ciento). LC/MS = 221.1 (M+H), LC = 2.235 minutos.

Síntesis de 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona



A una solución del 3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes), trifenil-fosfina (1.5 equivalentes), y ftalimida (1.5 equivalentes) en tetrahidrofurano (0.3 M) a 0°C, se le agregó por goteo (E)-diazen-1,2-dicarboxilato de diterbutilo (1.5 equivalentes). La reacción se agitó a 0°C durante 2 horas. Se concentró a sequedad al vacío, entonces se purificó el producto crudo mediante cromatografía en columna de gel de sílice, eluyendo con EtOAc y hexanos (1:1 con metanol al 5 por ciento), para proporcionar la 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona (63 por ciento de rendimiento). LC/MS = 350.3 (M+H), LC = 3.936 minutos.

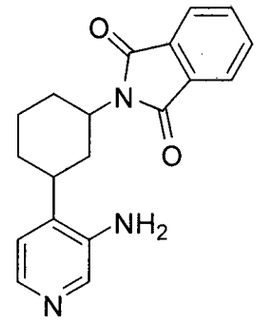
Síntesis de 2-(3-(3-amino-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona



A una solución de la 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona (1.0 equivalentes) en AcOH (0.38 M), se le agregó Fe (6.0 equivalentes), y la reacción se agitó a temperatura ambiente durante 2 horas. Se filtró, luego se lavó con metanol, y el filtrado se concentró. Al producto crudo se le agregó acetato de etilo y $NaHCO_3$ saturado, los orgánicos se

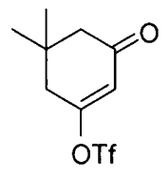
secaron con Na_2SO_4, y se concentraron, para dar la 2-(3-(3-amino-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona como una goma amarilla espesa en un 96 por ciento de rendimiento. LC/MS = 320.0 (M+H), LC = 2.410 minutos.

Síntesis de 2-(3-(3-amino-piridin-4-il)-ciclohexil)-isoindolina-1,3-diona



A una solución de la 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolina-1,3-diona (1.0 equivalentes) en ácido acético (0.1 M), se le agregó Pd/C al 10 por ciento (0.2 equivalentes), y la reacción se agitó bajo un globo de H_2. Después de 3 días, la reacción se filtró a través de Celite, se lavó con acetato de etilo y metanol, el filtrado se diluyó con acetato de etilo, y se lavó dos veces con Na_2CO_3 2M saturado. La fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró. El material crudo se trituró con hexanos y acetato de etilo, para proporcionar la 2-(3-(3-amino-piridin-4-il)-ciclohexil)-isoindolina-1,3-diona en un 73 por ciento de rendimiento. LC/MS = 322.2 (M+H), Rt = 0.64 minutos.

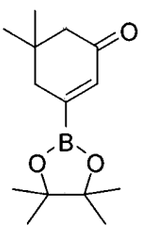
Síntesis de trifluoro-metan-sulfonato de 5,5-dimetil-3-oxociclohex-1-enilo



En un matraz de fondo redondo de 3 cuellos, se disolvió 5,5-dimetil-ciclohexano-1,3-diona (1.0 equivalentes) en dicloro-metano (0.2 M). Se le agregó carbonato de sodio (1.1 equivalentes), y la mezcla se enfrió con agitación magnética sobre un baño de hielo/sal/agua a aproximadamente -5°C bajo N_2. Se agregó por goteo triflato anhidro (1.05 equivalentes) diluido en dicloro-metano por medio del embudo de adición durante 90 minutos. Al completarse la adición, la reacción se agitó a aproximadamente 0°C durante 1 hora. De acuerdo con la LCMS y ^1H RMN, todavía hay un material de partida restante. Se le agregaron carbonato de sodio adicional (0.51 equivalentes) y triflato anhidro (0.50 equivalentes). Después de 2 horas, la mezcla se filtró a través de un embudo de vidrio fritado grueso (la torta se lavó con dicloro-metano), se transfirió a un matraz Erlenmeyer, se apagó mediante la adición cuidadosa de bicarbonato de sodio acuoso saturado con agitación vigorosa hasta un pH = 7, se transfirió a un embudo de separación, y las capas se separaron. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró, para dar el trifluoro-metan-sulfonato de 5,5-dimetil-

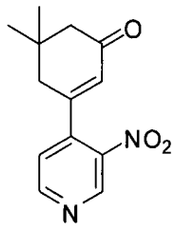
3-oxociclohex-1-enilo, el cual se utilizó para el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+=273.1, Rt=1.03 minutos.

Síntesis de 5,5-dimetil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona



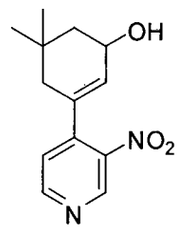
Todos los reactivos de trifluoro-metan-sulfonato de 5,5-dimetil-3-oxociclohex-1-enilo (1.0 equivalentes), acetato de potasio (3.0 equivalentes), y bis-(pinacolato)-diboro (2.0 equivalentes) se agregaron a 1,4-dioxano (0.2 M) en un matraz de fondo redondo, y se desgasificó mediante el burbujeo de N_2 a través de la mezcla durante 10 minutos. Se agregó $PdCl_2$(dppf) – aducción de dicloro-metano (0.03 equivalentes), y la reacción se calentó a 80°C ajustándose con un condensador de reflujo sobre un baño de aceite bajo N_2 durante la noche. La mezcla se enfrió a temperatura ambiente, se filtró a través de un embudo de vidrio fritado grueso, y la torta se enjuagó con 1,4-dioxano, para dar la 5,5-dimetil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona en 1,4-dioxano, que se utilizó para el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+(ácido borónico) = 169.1, Rt = 0.50 minutos.

Síntesis de 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona



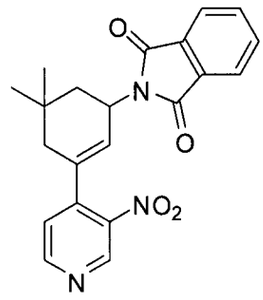
El éster de boronato de 5,5-dimetil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona (1.0 equivalentes) se disolvió en 1,4-dioxano en un matraz de fondo redondo, y se desgasificó mediante burbujeo de N_2 a través de la solución durante 30 minutos. Se agregaron 4-cloro-3-nitro-piridina (1.3 equivalentes) y carbonato de sodio acuoso 2M (2.0 equivalentes), se burbujeó N_2 a través de los mismos durante 10 minutos, y entonces se le agregó $PdCl_2$(dppf) - dicloro-metano (0.05 equivalentes). La mezcla de reacción se agitó a 110°C durante 2 horas. La mezcla se le agregó a EtOAc y agua. La mezcla resultante se filtró a través de Celite, y la torta se lavó con EtOAc. La capa orgánica se separó, y la fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (eluido con EtOAc:Hexanos = 1:10 a 2:1), para dar la 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (46.7 por ciento en tres pasos). LC/MS (*m/z*): MH^+ = 247.2, Rt = 0.79 minutos.

Síntesis de 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol



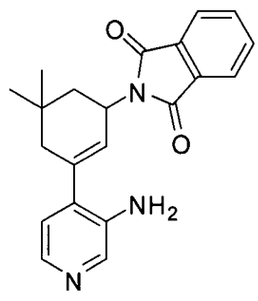
A una solución de la 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (1.0 equivalentes), y $CeCl_3$-$7H_2O$ (1.2 equivalentes) en metanol (0.2 M), se le agregó $NaBH_4$ (1.0 equivalentes) a 0°C. La solución se agitó durante 1 hora, y entonces se apagó mediante la adición de 5 mililitros de agua. Los volátiles se removieron al vacío, y el residuo se dividió entre EtOAc y H_2O. La capa orgánica se separó y se lavó con salmuera. La fase acuosa combinada se retro-extrajo con EtOAc, y la fase orgánica se lavó con salmuera. Los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, y se concentraron. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar el 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (74 por ciento). LC/MS (*m/z*): MH^+ = 249.2, R t= 0.76 minutos.

Síntesis de 2-(5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolin-1,3-diona



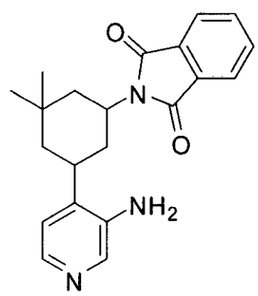
A una solución homogénea de 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes), trifenil-fosfina (1.5 equivalentes), y ftalimida (1.5 equivalentes) en tetrahidrofurano (0.2 M) enfriada a 0°C, se le agregó azodicarboxilato de diterbutilo (1.5 equivalentes) en tetrahidrofurano. La mezcla se agitó a 0°C durante 2 horas. La reacción se concentró al vacío. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar la 2-(5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolin-1,3-diona (99 por ciento). LC/MS (*m/z*): MH^+=378.2, Rt=1.10 minutos.

Síntesis de 2-(3-(3-amino-piridin-4-il)-5,5-dimetil-ciclohex-2-enil)-isoindolin-1,3-diona



Una solución de 2-(5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolin-1,3-diona (1 equivalente) en ácido acético (0.1 M) se purgó con nitrógeno durante 10 minutos. Entonces se agregó Pd/C al 10 por ciento (0.10 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante la noche bajo una atmósfera de hidrógeno. Los sólidos se removieron mediante filtración sobre Celite, y entonces se enjuagaron con EtOAc y metanol. El filtrado se concentró, se diluyó con EtOAc, y se lavó 2 veces con Na_2CO_3 2M acuoso saturado. La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar la 2-(3-(3-amino-piridin-4-il)-5,5-dimetil-ciclohex-2-enil)-isoindolin-1,3-diona (89 por ciento). LC/MS (*m/z*): MH^+ = 348.3, Rt = 0.79 minutos.

Síntesis de 2-(5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolin-1,3-diona

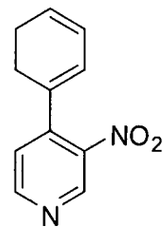


Una solución de la 2-(3-(3-amino-piridin-4-il)-5,5-dimetil-ciclohex-2-enil)-isoindolin-1,3-diona (1.0 equivalentes) en ácido

acético (0.1 M) se purgó con nitrógeno durante 10 minutos. Entonces se agregó Pd/C al 10 por ciento (0.1 equivalentes). La mezcla de reacción se agitó a 45°C, en una atmósfera de hidrógeno a 14 kg/cm^2 en una bomba de acero durante la noche, y a 65°C, a 14 kg/cm^2 durante 5 horas. Los sólidos se removieron mediante filtración sobre Celite, y entonces se enjuagaron con EtOAc y metanol. El filtrado se concentró, se diluyó con EtOAc, y se lavó 2 veces con Na_2CO_3 2M acuoso saturado. La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar la 2-(5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolin-1,3-diona (53 por ciento). LC/MS (*m/z*): MH^+ = 350.3, Rt = 0.78 minutos. La 2-((1*R*,5*R*)-5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolin-1,3-diona y la 2-((1*S*,5*S*)-5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolin-1,3-diona enantioméricamente puras se resolvieron mediante HPLC quiral. (Para el análisis R_t = 7.526 minutos y 13.105 minutos, respectivamente; hexanos:etanol = 80:20 (volumen : volumen), Chiralcel OJ-H 100 x 4.6 milímetros a 1 mililitro/minuto. Para la separación de preparación, hexanos:etanol = 80:20 (volumen : volumen), Chiralcel OJ-H (250 x 20 milímetros a 20 mililitros/minuto). ^1H RMN ($CDCl_3$): δ 8.04 (s, 1H), 8.00 (d, 1H), 7.82 (m, 2H), 7.71 (m, 2H), 7.06 (d, 1H), 4.54 (m, 1H), 3.71 (m, 2H), 2.89 (m, 1H), 2.23-2.44 (m, 2H), 1.90 (m, 1H), 1.20-1.60

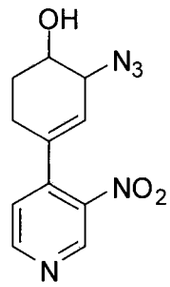
(m, 3H), 1.18 (s, 3H), 1.07 (s, 3H).

Síntesis de 4-(ciclohexa-1,3-dienil)-3-nitro-piridina



A una solución del 3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes), se le agregaron dioxano (0.18M) y p-TSA (1.1 equivalentes). La solución se calentó a 100°C durante 4 horas. Se enfrió a temperatura ambiente, se procesó con $NaHCO_3$ saturado y acetato de etilo, la fase orgánica se secó con Na_2SO_4 y se concentró. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con el 100 por ciento de dicloro-metano, para dar la 4-(ciclohexa-1,3-dienil)-3-nitro-piridina como un aceite amarillo (27 por ciento de rendimiento). LCMS (*m/z*): 203.1 (MH^+), LC R_t = 3.53 minutos, H-RMN ($CDCl_3$): 9.02 (s, 1H), 8.70 (d, J=5.3, 1H), 7.30 (d, J=5.3, 1H), 6.15-6.17 (m, 1H), 6.02-6.11 (m, 2H), 2.35-2.38 (m, 4H).

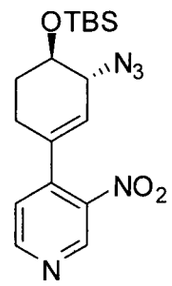
Síntesis de (+/-)-2-azido-4-(3-nitro-piridin-4-il)-ciclohex-3-enol



A una solución de la 4-(ciclohexa-1,3-dienil)-3-nitro-piridina (1.0 equivalentes) en dicloro-metano (0.1 M), se le agregó $NaHCO_3$ (1.2 equivalentes), para dar una solución amarilla. Se enfrió a 0°C, y entonces se agregó m-CPBA (1.0 equivalentes) a la solución toda a la vez como un sólido. La reacción se agitó a 0°C durante 3.5 horas. Se monitoreó mediante tanto TLC como LC/MS. El producto se ioniza como M+H = 237 (diol); Rt = 0.41 minutos en la UPLC. La reacción se apagó con $NaHCO_3$ saturado, y entonces se extrajo con dicloro-metano (3 veces). La fase orgánica se secó adicionalmente con salmuera, luego con Na_2SO_4, se filtró, y se concentró, para dar el epóxido crudo como un aceite amarillo, el cual se utilizó sin mayor purificación.

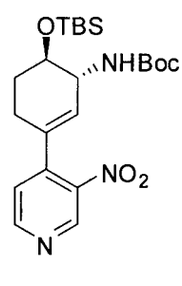
A una solución del material crudo anterior en EtOH y agua (3:1) (solución amarilla nebulosa), se le agregaron NaN_3 (2.0 equivalentes), y NH_4Cl (2.0 equivalentes), para dar una solución color naranja transparente. La reacción se agitó durante 16 horas, y entonces se concentró. Se agregaron EtOAc y agua, la fase orgánica se secó adicionalmente con $MgSO_4$ y se concentró, para dar un aceite color café. El aceite se cargó en gel de sílice, y se purificó mediante cromatografía en columna (ISCO, del 0 al 50 por ciento de EtOAc), para dar el (+/-)-2-azido-4-(3-nitro-piridin-4-il)-ciclohex-3-enol como un aceite amarillo (44 por ciento, en 2 pasos). LCMS (*m/z*) = 262 (MH^+), LC R_t = 2.35 minutos.

Síntesis de (+/-)-4-(3-azido-4-(ter-butil-dimetil-sililoxi)-ciclohex-1-enil)-3-nitro-piridina



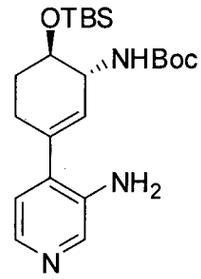
A una solución del (+/-)-2-azido-4-(3-nitro-piridin-4-il)-ciclohex-3-enol (1.0 equivalentes) en dicloro-metano (0.15M), se le agregaron TBSCl (2.0 equivalentes), imidazol (2.0 equivalentes) y DMAP (0.1 equivalentes) a temperatura ambiente. Después de 18 horas, se agregó agua, los orgánicos se secaron con salmuera, luego con Na_2SO_4, y se concentraron. El material crudo se cargó en gel de sílice, y se purificó por medio de cromatografía en columna (ISCO) eluyendo con acetato de etilo y hexanos (20 por ciento). Se obtuvo la (+/-)-4-(3-azido-4-(ter-butil-dimetil-sililoxi)-ciclohex-1-enil)-3-nitro-piridina como un aceite amarillo en un 60 por ciento de rendimiento. LCMS (*m/z*): 376.3 (MH^+), LC R_t = 5.848 minutos.

Síntesis de (+/-)-6-(ter-butil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo



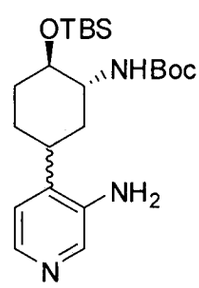
En un matraz de fondo redondo se agregaron (+/-)-4-(3-azido-4-(ter-butil-dimetil-sililoxi)-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) y piridina (0.1M), para dar una solución amarilla. Se agregó hidróxido de amonio (10:1 de piridina: hidróxido de amonio), seguido por PMe_3 (3.0 equivalentes). La reacción cambió a un color café oscuro después de 10 minutos. Se agitó a temperatura ambiente durante 1.5 horas. Se apagó mediante la adición de EtOH, y se concentró. Se repitió 2 veces más. Al producto crudo se le agregaron $NaHCO_3$ saturado y dioxano (1:1, 0.1M). Se agregó Boc_2O (1.0 equivalentes). Se agitó durante una hora a temperatura ambiente. Se lavó con H_2O y EtOAc, la fase orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó por medio de cromatografía en columna del gel de sílice (ISCO, 5:1 de Hex/EtOAc). Las fracciones recolectadas puras se concentraron, para dar el (+/-)-6-(ter-butil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo como una espuma. LCMS (*m/z*): 450.3 (MH^+), LC R_t = 5.83 minutos.

Síntesis de (+/-)-3-(3-amino-piridin-4-il)-6-(ter-butil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de ter-butilo



A una solución del (+/-)-6-(ter-butil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) en AcOH (0.18 M), se le agregó Fe (6.0 equivalentes), y la reacción se agitó durante 20 horas. Se procesó diluyendo la reacción con metanol, se filtró, y el filtrado se concentró. Al producto crudo se le agregó acetato de etilo y $NaHCO_3$ saturado, los orgánicos se secaron con sulfato de sodio y se concentraron, para dar el (+/-)-3-(3-amino-piridin-4-il)-6-(ter-butil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de ter-butilo como un aceite amarillo en un 94 por ciento de rendimiento. LCMS (*m/z*): 420.3 (MH^+), LC R_t = 3.88 minutos.

Síntesis de (+/-)-5-(3-amino-piridin-4-il)-2-(ter-butil-dimetil-sililoxi)-ciclohexil-carbamato de ter-butilo



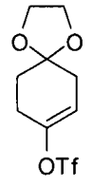
A una solución del (+/-)-3-(3-amino-piridin-4-il)-6-(ter-

butil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) en metanol (0.1M), se le agregó Pd/C (al 20 por ciento en peso), y la reacción se agitó bajo un globo de hidrógeno durante 18 horas. La LC/MS de la reacción indicó una mezcla de diaestereómeros, la reacción se filtró, se lavó con EtOAc, y el filtrado se concentró. El material crudo se purificó por medio de HPLC de preparación (en sulfóxido de dimetilo), y las fracciones puras se combinaron, se neutralizaron con $NaHCO_3$ sólido, se extrajeron con acetato de etilo, se lavaron con salmuera, se secaron bajo Na_2SO_4, y se concentraron, para dar el producto A (8 por ciento de rendimiento) y el producto B (51 por ciento de rendimiento).

Producto A: LCMS (*m/z*): 422.4 (MH^+), LC R_t = 3.75 minutos.

Producto B: LCMS (*m/z*): 422.4 (MH^+), LC R_t = 3.94 minutos.

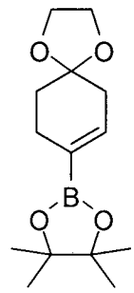
Síntesis de trifluoro-metan-sulfonato de 1,4-dioxaespiro-[4.5]-dec-7-en-8-ilo



La 1,4-dioxaespiro-[4.5]-decan-8-ona (1.0 equivalentes) se disolvió en éter (0.1 M), y se agitó a -15°C; entonces se agregó NaHMDS 1M (1.05 equivalentes), y se agitó durante 70 minutos. Luego se agregó Tf_2O (1.05 equivalentes), y la reacción se dejó calentar lentamente hasta la temperatura

ambiente. La mezcla se agitó durante 28 horas, se lavó con $NaHCO_3$ acuoso saturado, y luego con agua. Las capas acuosas se combinaron y se extrajeron con éter. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, y se concentraron. El residuo se purificó mediante columna (etil-éter : hexanos = 1 : 4), para dar el trifluoro-metan-sulfonato de 1,4-dioxaespiro-[4.5]-dec-7-en-8-ilo (65 por ciento). LC/MS (*m/z*): MH^+ = 289.0, Rt = 0.97. HPLC Rt = 3.77 minutos.

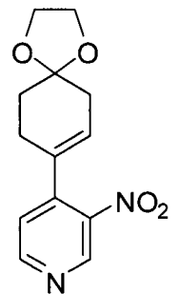
Síntesis de 4,4,5,5-tetrametil-2-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-1,3,2-dioxaborolano



Una solución del trifluoro-metan-sulfonato de 1,4-dioxaespiro-[4.5]-dec-7-en-8-ilo (1.0 equivalentes) en dioxano (0.5 M) se purgó con nitrógeno durante 30 minutos. Entonces se agregaron 4,4,4',4',5,5,5',5'-octa-metil-2,2'-bi-(1,3,2-dioxaborolano) (1.0 equivalentes), KOAc (3.0 equivalentes), $Pd(dppf)Cl_2$-DCM (0.2 equivalentes), y la solución se agitó en una bomba sellada a 80°C. La reacción se filtró sobre una almohadilla de Celite, entonces al filtrado se le agregó acetato de etilo, y se lavó con salmuera, se secó sobre $MgSO_4$, se

filtró, y se concentró. El residuo se purificó mediante columna (acetato de etilo : hexanos = 1 : 1), para dar el 4,4,5,5-tetrametil-2-(1,4-dioxaespiro-[4.5]-dec-7-en-8-il)-1,3,2-dioxaborolano (95 por ciento). LC/MS (*m/z*): MH^+ = 267.1, Rt = 0.95 minutos.

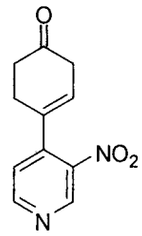
Síntesis de 3-nitro-4-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-piridina



Una solución de DME (0.2 M), y carbonato de sodio acuoso 2M (1.7 equivalentes) se purgó con nitrógeno durante 20 minutos. Entonces se agregaron 4-cloro-3-nitro-piridina (1.6 equivalentes), 4,4,5,5-tetrametil-2-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-1,3,2-dioxaborolano (1.0 equivalentes), $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), y se agitaron en una bomba sellada a 110°C. La reacción se agitó a esa temperatura durante 3.5 horas. La reacción se diluyó con acetato de etilo, se lavó con agua, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (acetato de etilo : hexanos = 1 : 1 con metanol al 10 por ciento), para dar la 3-nitro-4-(1,4-dioxaespiro-[4.5]-dec-7-en-8-il)-piridina (83 por

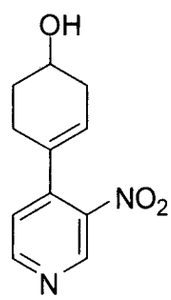
ciento). LC/MS (*m/z*): MH^+ = 263.2, Rt = 0.71 minutos.

Síntesis de 4-(3-nitro-piridin-4-il)-ciclohex-3-enona



Una mezcla de la 3-nitro-4-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-piridina (1.0 equivalentes) en ácido trifluoro-acético al 20 por ciento en CH_2Cl_2 (0.2 M) se agitó a temperatura ambiente durante la noche. Los solventes se removieron bajo presión reducida. El residuo se disolvió con acetato de etilo (200 mililitros), y se lavó con $NaHCO_3$ saturado (30 mililitros) y NaCl saturado (30 mililitros). La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró, para dar la 4-(3-nitro-piridin-4-il)-ciclohex-3-enona (85 por ciento). El producto crudo se utilizó para el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 218.9, Rt = 0.60 minutos.

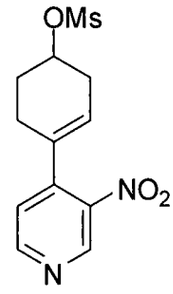
Síntesis de 4-(3-nitro-piridin-4-il)-ciclohex-3-enol



A una solución de la 4-(3-nitro-piridin-4-il)-ciclohex-3-

enona (1.0 equivalentes) en metanol (0.2 M), se le agregó borohidruro de sodio (1.8 equivalentes) a 0°C. La mezcla de reacción se agitó a 0°C durante 2 horas. El metanol se removió bajo presión reducida. El residuo se disolvió con acetato de etilo (200 mililitros), y se lavó con NaCl saturado (30 mililitros). La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró, para dar el 4-(3-nitro-piridin-4-il)-ciclohex-3-enol (85 por ciento). El producto crudo se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 221.0, Rt = 0.55 minutos.

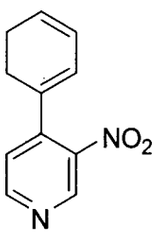
Síntesis de metan-sulfonato de 4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



A una solución del 4-(3-nitro-piridin-4-il)-ciclohex-3-enol (1.0 equivalentes), y di-isopropil-etil-amina (2.5 equivalentes) en CH_2Cl_2 (0.15 M), se le agregó cloruro de metan-sulfonilo (1.8 equivalentes) a 0°C. La mezcla de reacción se agitó a 0°C durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (200 mililitros), y se lavó con NaCl saturado (30 mililitros). La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró,

para dar el metan-sulfonato de 4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (93 por ciento). El residuo se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 299.0, Rt = 0.70 minutos.

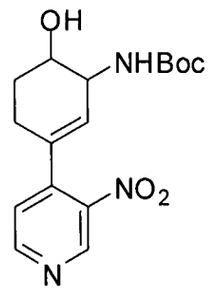
Síntesis de 4-(ciclohexa-1,3-dienil)-3-nitro-piridina



A una solución de metan-sulfonato de 4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en tetrahidrofurano (0.1 M), se le agregó DBU (1.8 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (200 mililitros), y se lavó con NaCl saturado (30 mililitros). La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar la 4-(ciclohexa-1,3-dienil)-3-nitro-piridina. LC/MS (*m/z*): MH^+ = 203.2, Rt = 0.85 minutos.

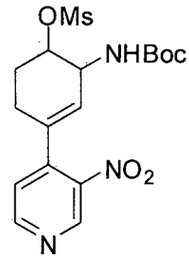
151

Síntesis de (+/-)-6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo



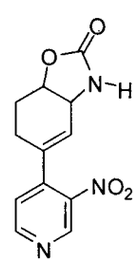
A una solución del (+/-)-2-azido-4-(3-nitro-piridin-4-il)-ciclohex-3-enol (1.0 equivalentes) en piridina y NH_4OH (8:1, 0.23 M), se le agregó trimetil-fosfina (3.0 equivalentes) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 3 horas. Los solventes se removieron. Al residuo se le agregó etanol. Entonces se removió el etanol al vacío para asegurar la remoción del amoníaco totalmente. El residuo se disolvió en 1,4-dioxano y bicarbonato de sodio acuoso saturado, y entonces se agregó a la mezcla el Boc_2O (1.0 equivalentes) en tetrahidrofurano. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con NaCl saturado. La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar el (+/-)-6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (82 por ciento). LC/MS (*m/z*): MH^+ = 336.0, Rt = 0.71 minutos.

Síntesis de (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



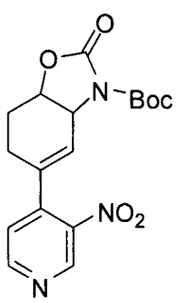
A una solución de (+/-)-6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) y trietil-amina (1.5 equivalentes) en CH_2Cl_2 (0.2 M), se le agregó cloruro de metan-sulfonilo (1.2 equivalentes) a 0°C. La mezcla se agitó durante 2 horas a esa temperatura. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con NaCl saturado. La fase orgánica se secó con $MgSO_4$, se filtró, y se concentró, para dar el (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (85 por ciento), el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 414.0, Rt = 0.82 minutos.

Síntesis de (+/-)-5-(3-nitro-piridin-4-il)-3,3a,7,7a-tetrahidro-benzo-[d]-oxazol-2(6H)-ona



La mezcla de (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en piridina (0.21 M) se agitó a 110°C durante 10 minutos en microondas. La piridina se removió bajo presión reducida. El residuo se disolvió en acetato de etilo, y se lavó con NaCl saturado. La fase orgánica se secó con $MgSO_4$, se filtró, y se concentró, para dar la (+/-)-5-(3-nitro-piridin-4-il)-3,3a,7,7a-tetrahidro-benzo-[d]-oxazol-2(6H)-ona (85 por ciento), la cual se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 262.1, Rt = 0.49 minutos.

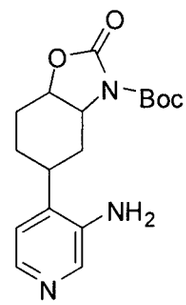
Síntesis de (+/-)-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



A una solución de la (+/-)-5-(3-nitro-piridin-4-il)-3,3a,7,7a-tetrahidro-benzo-[d]-oxazol-2(6H)-ona (1.0 equivalentes), trietil-amina (1.8 equivalentes), y una cantidad catalítica de DMAP en CH_2Cl_2 (0.19 M), se le agregó dicarbonato de diterbutilo (1.2 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (100 mililitros), y se

lavó con NaCl saturado (30 mililitros). La fase orgánica se secó con $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar el (+/-)-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (98 por ciento). LC/MS (*m/z*): MH^+ = 306.0, Rt = 0.75 minutos.

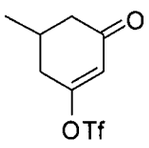
Síntesis de (+/-)-5-(3-amino-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



A una solución del (+/-)-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (1.0 equivalentes) en metanol y acetato de etilo (1;1, 0.1 M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La mezcla resultante se agitó bajo una atmósfera de H_2 durante 6 horas. El sólido se removió mediante filtración. El filtrado se concentró bajo presión reducida, para dar el (+/-)-5-(3-amino-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (87 por ciento), el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+ = 334.1, Rt =

0.51 minutos.

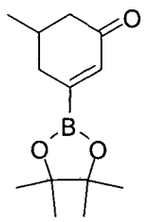
Síntesis de trifluoro-metan-sulfonato de 5-metil-3-oxo-ciclohex-1-enilo



A una solución de la 5-metil-ciclohexano-1,3-diona (1.0 equivalentes) en dicloro-metano (0.5M), se le agregó Na_2CO_3 (1.1 equivalentes), y se enfrió a 0°C. Se agregó por goteo Tf_2O (1.0 equivalentes) en dicloro-metano (5.0 M) durante 1 hora a 0°C bajo una atmósfera de nitrógeno. Después de la adición, la reacción se agitó durante 1 hora a temperatura ambiente (solución color rojo oscuro). La solución se filtró, y el filtrado se apagó mediante la adición cuidadosa de $NaHCO_3$ saturado con agitación vigorosa hasta un pH = 7. La solución se transfirió a un embudo de separación, y las capas se separaron. La capa orgánica se lavó con salmuera, se secó con Na_2SO_4, se filtró, se concentró al vacío, y se secó bajo un alto vacío durante 15 minutos, para proporcionar el trifluoro-metan-sulfonato de 5-metil-3-oxo-ciclohex-1-enilo como un aceite amarillo claro en un 78 por ciento de rendimiento. El triflato se descompone en el almacenamiento, y se debe utilizar inmediatamente para la siguiente reacción. LC/MS = 259.1/300.1 (M+H y $M+CH_3CN$); Rt = 0.86 minutos, LC = 3.84

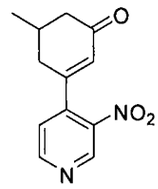
minutos. ^{1}H-RMN (400 MHz, $CDCl_3$) δ ppm: 6.05 (s, 1H), 2.70 (dd, J=17.2, 4.3, 1H), 2.53 (dd, J=16.6, 3.7, 1H), 2.48-2.31 (m, 2H), 2.16 (dd, J=16.4, 11.7, 1H), 1.16 (d, J=5.9, 3H).

Síntesis de 5-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona



A una solución del trifluoro-metan-sulfonato de 5-metil-3-oxo-ciclohex-1-enilo (1.0 equivalentes) en dioxano desgasificado (0.7 M), se le agregaron bis-(pinacolato)-diboro (2.0 equivalentes), KOAc (3.0 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.03 equivalentes). La reacción se calentó a 80°C durante 10 horas (el calentamiento inicial a gran escala da como resultado la formación exotérmica de una espuma color naranja encima de la solución, y se debe remover el baño de calentamiento hasta que se retraiga la espuma, volviendo a calentar hasta 80°C, que en este punto parece ser fina), entonces se enfrió a temperatura ambiente, y se filtró a través de un embudo de vidrio de frita grueso. La torta se enjuagó con más dioxano, y la solución filtrada se utilizó para el siguiente paso sin mayor purificación. LC/MS = 155.1 (M+H de ácido borónico); Rt = 0.41 minutos, LC = 1.37 minutos.

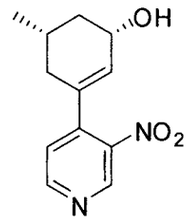
Síntesis de 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona



A una solución de la 5-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona (1.0 equivalentes) en dioxano desgasificado (0.5 M), y Na_2CO_3 2M (2 equivalentes), se le agregó 4-cloro-3-nitro-piridina (1.3 equivalentes), y Pd(dppf)Cl_2-DCM (0.05 equivalentes). La reacción se colocó bajo un condensador de reflujo, y se calentó en un baño de aceite hasta 110°C durante 1 hora. Se enfrió a temperatura ambiente, se filtró a través de una almohadilla de Celite, se lavó la almohadilla con acetato de etilo, y el filtrado se concentró al vacío. El residuo se bombeó adicionalmente a 80°C sobre un evaporador giratorio durante una hora para remover los subproductos de boronato (M+H = 101) por medio de sublimación. El residuo se dividió entre salmuera y acetato de etilo, y las capas se separaron; la fase acuosa se extrajo adicionalmente con acetato de etilo (4 veces), los orgánicos se combinaron, se secaron sobre sulfato de sodio, se filtraron, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice, cargando en dicloro-metano y eluyendo con del 2 al 50 por ciento de acetato de etilo y hexanos. Las fracciones puras se concentraron al vacío, para proporcionar un aceite color naranja. El aceite se colocó bajo

un alto vacío (aproximadamente 500 mtorr) con cristales de siembra durante la noche, para proporcionar un sólido color naranja. El sólido se purificó adicionalmente por medio de trituración en hexanos, para proporcionar la 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (48 por ciento en 2 pasos). LC/MS = 233.2 (M+H); Rt = 0.69 minutos, LC = 2.70 minutos. ^{1}H-RMN (400 MHz, $CdCl_3$) δ ppm: 9.31 (s, 1H), 8.88 (d, J=5.1, 1H), 7.30 (d, J=5.1, 1H), 6.00 (d, J=2.4, 1H), 2.62 (dd, J=16.4, 3.5, 1H), 2.53-2.34 (m, 3H), 2.23 (dd, J=16.1, 11.7, 1H), 1.16 (d, J=6.3, 3H).

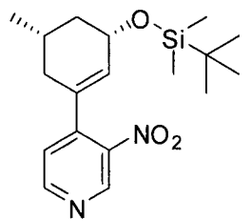
Síntesis de cis-(+/-)-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol



A una solución de la 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (1.0 equivalentes) en EtOH (0.3 M), se le agregó $CeCl_3$-$7H_2O$ (1.2 equivalentes). La reacción se enfrió a 0°C, y entonces se agregó en porciones $NaBH_4$ (1.2 equivalentes). Se agitó durante 1 hora a 0°C, entonces se apagó mediante la adición de agua, se concentró para remover el EtOH, se agregó EtOAc, los orgánicos se extrajeron, se lavaron con salmuera, luego se secaron con Na_2SO_4, se

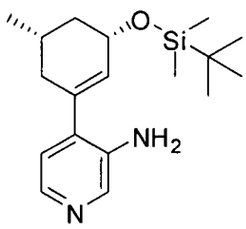
filtraron, y se concentraron, para proporcionar el cis-(+/-)-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (94 por ciento). LC/MS = 235.2 (M+H), LC = 2.62 minutos.

Síntesis de 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina



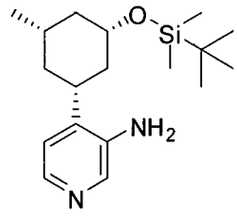
A una solución del 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en N,N-dimetil-formamida (0.5 M), se le agregó imidazol (4.0 equivalentes), y TBDMSCl (2.5 equivalentes). Después de agitar durante 18 horas, la solución se dividió en porciones entre EtOAc y H_2O, y se separó. Después de lavar adicionalmente con H_2O (3 veces), y NaCl (saturado), el secado sobre $MgSO_4$, el filtrado, y la remoción de los solventes, se obtuvo la 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (85 por ciento). LC/MS = 349.2 (M+H), LC = 5.99 minutos.

Síntesis de 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-amina



Una solución heterogénea de 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes), y hierro (6.0 equivalentes) en ácido acético, en una concentración de 0.4 M, se agitó vigorosamente durante 2 horas. La mezcla entonces se pasó a través de una almohadilla de Celite, eluyendo con metanol. Después de la remoción de los volátiles al vacío, el residuo se disolvió en EtOAc, se lavó con Na_2CO_3 (saturado), NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y los volátiles se removieron al vacío, proporcionando la 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-amina (78 por ciento). LCMS (*m/z*): 319.3 (MH^+); LC R_t = 3.77 minutos.

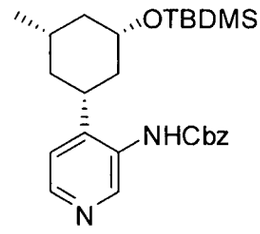
Síntesis de 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina



A una solución de la 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 15 horas. En este tiempo, la

mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina (90 por ciento). LCMS (*m/z*): 321.3 (MH^+); LC R_t = 3.85 minutos.

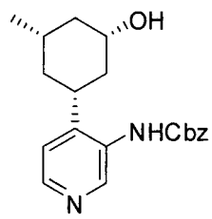
Síntesis de cis-(+/-)-4-3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo



A una solución de cis-(+/-)-4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina en dicloro-metano en una concentración de 0.5 M, se le agregó 2,5-dioxo-pirrolidin-1-il-carbonato de bencilo (1.1 equivalentes), y DMAP (0.05 equivalentes). Después de agitar durante 16 horas a temperatura ambiente, se agregaron 2,5-dioxo-pirrolidin-1-il-carbonato de bencilo (0.55 equivalentes), y DMAP (0.03 equivalentes) adicionales. Después de agitar durante 24 horas adicionales a temperatura ambiente, se agregaron 2,5-dioxo-pirrolidin-1-il-carbonato de bencilo (0.1 equivalentes), y DMAP (0.03 equivalentes) adicionales. Después de agitar durante 18 horas más, la solución se dividió entre EtOAc y Na_2CO_3 (saturado), y se separó. Después de un lavado adicional con

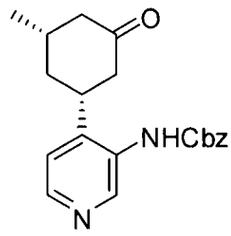
Na_2CO_3 (saturado) (2 veces), y NaCl (saturado), el secado sobre $MgSO_4$, la filtración, y la remoción de los solventes, se obtuvo el cis-(+/-)-4-3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo. El material crudo se utilizó como estaba. LC/MS = 455.3 (M+H), LC = 4.39 minutos.

Síntesis de cis-(+/-)-4-(3-hidroxi-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo



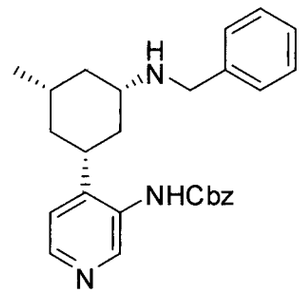
Una solución del cis-(+/-)-4-3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo en 1:2:1 de HCl 6N / THF / MeOH, en una concentración de 0.1 M, se agitó a temperatura ambiente durante 6 horas. El pH se ajustó entonces a un pH = 7 mediante la adición de NaOH 6N, y los volátiles se removieron al vacío. La capa acuosa se extrajo con EtOAc, y la capa orgánica se lavó con NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y después de la remoción de los volátiles al vacío, se obtuvo el cis-(+/-)-4-(3-hidroxi-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo. El material crudo se utilizó como estaba. LC/MS = 341.2 (M+H), LC = 2.38 minutos.

Síntesis de cis-(+/-)-4-(3-metil-5-oxo-ciclohexil)-piridin-3-il-carbamato de bencilo



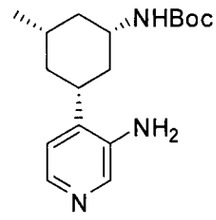
A una solución a 0°C de cis-(+/-)-4-(3-hidroxi-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo en CH_2Cl_2 húmedo, en una concentración de 0.16 M, se le agregó peryodinano Dess-Martin (1.5 equivalentes), y la solución se agitó durante 18 horas a medida que se calentaba hasta la temperatura ambiente. La solución se dividió entre EtOAc y 1:1 de $Na_2S_2O_3/NaHCO_3$ (saturado) al 10 por ciento, y se separó. Después de un lavado adicional con 1:1 de $Na_2S_2O_3/NaHCO_3$ (saturado) al 10 por ciento (2 veces), y NaCl (saturado), el secado sobre $MgSO_4$, la filtración, la remoción de los solventes, y la purificación mediante cromatografía en gel de sílice (del 75 al 100 por ciento de EtOAc/hexanos), se obtuvo el cis-(+/-)-4-(3-metil-5-oxo-ciclohexil)-piridin-3-il-carbamato de bencilo como un sólido blanco (53 por ciento, 5 pasos). LC/MS = 339.2 (M+H).

Síntesis de cis-(+/-)-4-(-3-(bencil-amino)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo



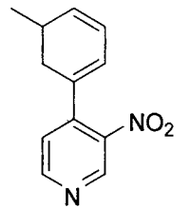
Una solución del cis-(+/-)-4-(3-metil-5-oxo-ciclohexil)-piridin-3-il-carbamato de bencilo (1.0 equivalentes), y bencil-amina (3.0 equivalentes) en MeOH, en una concentración de 0.25 M, se agitó a temperatura ambiente durante 2 horas. Después de enfriarse en un baño a -78°C, se agregó $LiBH_4$ (1.1 equivalentes, 2.0 M en tetrahidrofurano), y la solución se dejó calentar a temperatura ambiente con agitación durante 16 horas. La solución se dividió entre EtOAc y $NaHCO_3$ (saturado), se separó, se lavó adicionalmente con $NaHCO_3$ (saturado), y NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y después de la remoción de los volátiles al vacío, se obtuvo el cis-(+/-)-4-(-3-(bencil-amino)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo como una mezcla de isómeros de 4:1, con todo *cis* como predominante LC/MS = 430.3 (M+H), LC = 0.62 minutos.

Síntesis de cis-(+/-)-(-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo



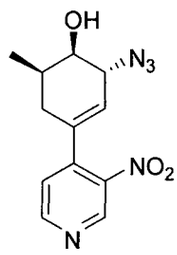
A una solución del cis-(+/-)-4-(-3-(bencil-amino)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo (1.0 equivalentes) en metanol, en una concentración de 0.07 M, se le agregó hidróxido de paladio al 20 por ciento sobre carbón (0.2 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la reacción se purgó con Ar, se agregó Boc_2O (1.0 equivalentes), y la solución se agitó durante 8 horas. Se agregó Boc_2O adicional (1.0 equivalentes), y la solución se agitó durante 16 horas más. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Después de la remoción de los volátiles al vacío, la purificación mediante cromatografía en gel de sílice (2.5-2.5 MeOH/CH_2Cl_2 con DIEA al 0.1 por ciento), y la recristalización a partir de EtOAc/hexanos al 10 por ciento, proporcionó el cis-(+/-)-(-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo (49 por ciento). LCMS (*m/z*): 306.3 (MH^+), LC R_t = 2.59 minutos. Se pudieron obtener los enantiómeros puros mediante cromatografía quiral.

Síntesis de (+/-)-4-(5-metil-ciclohexa-1,3-dienil)-3-nitro-piridina



A una solución del (+/-)-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en dioxano (0.1M), se le agregó p-TSA (1.0 equivalentes), y la reacción se agitó a 100°C durante 3 horas. La solución se enfrió a temperatura ambiente, entonces se pasó a través de una almohadilla de alúmina neutra eluyendo con EtOAc, para proporcionar la (+/-)-4-(5-metil-ciclohexa-1,3-dienil)-3-nitro-piridina como un aceite amarillo en un 68 por ciento de rendimiento. LC/MS = 217.1 (M+H), LC = 3.908 minutos.

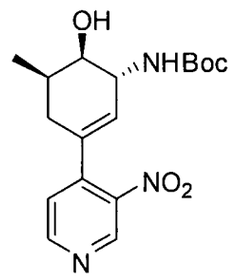
Síntesis de (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol



A una solución de la (+/-)-4-(5-metil-ciclohexa-1,3-dienil)-3-nitro-piridina (1.0 equivalentes) en dicloro-metano (0.1 M) a 0°C, se le agregó m-CPBA (1.1 equivalentes), y la reacción se

dejó calentar a temperatura ambiente. Después de 3 horas, la mezcla se apagó con $NaHCO_3$ saturado, se extrajo con diclorometano, y la fase orgánica se secó con sulfato de sodio, se filtró, y se concentró, para dar un aceite amarillo. El producto crudo se disolvió en etanol y agua (3:1, 0.1 M), y se agregaron azida de sodio (2.0 equivalentes), y cloruro de amonio (2.0 equivalentes). La reacción se agitó durante 4 horas, y entonces se concentró al vacío. Al producto crudo se le agregó acetato de etilo y agua, la fase orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para proporcionar el (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol como un aceite en un 49 por ciento de rendimiento. LC/MS = 276.1 (M+H), Rt = 0.71 minutos.

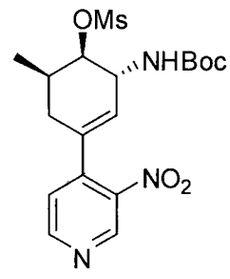
Síntesis de (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo



A una solución del (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol (1.0 equivalentes) en piridina e hidróxido

de amonio (8:1, 0.08 M), se le agregó trimetil-fosfina (3.0 equivalentes), y la solución color café se agitó a temperatura ambiente durante 2 horas. A la mezcla se le agregó etanol, y la solución se concentró al vacío (2 veces). La mezcla cruda se disolvió entonces en dioxano y $NaHCO_3$ saturado (1:1, 0.08 M), y se agregó Boc_2O (1.0 equivalentes). La solución se agitó a temperatura ambiente durante 2 horas, entonces se dividió entre acetato de etilo y agua. La fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para proporcionar el (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo en un 69 por ciento de rendimiento. LC/MS = 350.1 (M+H), Rt = 0.76 minutos.

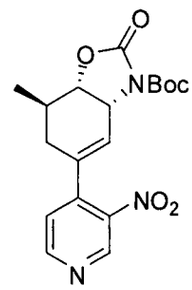
Síntesis de (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



A una solución del (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) en dicloro-metano (0.09 M), se le agregó trietil-

amina (1.5 equivalentes). La mezcla de reacción se enfrió a 0°C, y se agregó MsCl (1.2 equivalentes) a la reacción, y se agitó durante 3 horas. A la solución se le agregó agua, la fase orgánica se secó con sulfato de sodio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para dar el (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo como una espuma blanca en un 65 por ciento de rendimiento. LC/MS = 428.2 (M+H), Rt = 0.88 minutos.

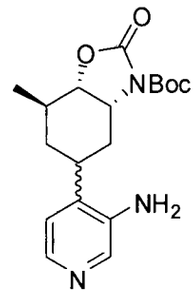
Síntesis de (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



Una solución del (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en piridina (0.2 M), en un recipiente de microondas, se calentó a 110°C durante 10 minutos. La solución color naranja se concentró entonces a sequedad, y se procesó mediante su división entre acetato de etilo y agua. La fase orgánica se secó con sulfato de sodio, se filtró, y se

concentró. El material crudo se disolvió en dicloro-metano (0.2 M), y se agregó trietil-amina (1.8 equivalentes) a la reacción, seguida por Boc_2O (1.2 equivalentes). Después de agitar a temperatura ambiente durante 40 minutos, la reacción se concentró al vacío y se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para dar el (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo como una espuma blanca en un 66 por ciento de rendimiento. LC/MS = 376.0 (M+H), Rt = 0.87 minutos.

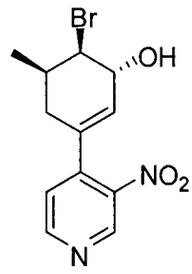
Síntesis de (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



A una solución del (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (1.0 equivalentes) en metanol y acetato de etilo (1:1, 0.07 M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes), y la reacción se agitó a temperatura ambiente bajo una atmósfera de hidrógeno. Al completarse de la reacción, la

solución se filtró a través de una almohadilla de Celite, se lavó con metanol y acetato de etilo, y el filtrado se concentró a sequedad al vacío, para dar el (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo como una mezcla de diaestereómeros en >99 por ciento de rendimiento. LC/MS = 348.2 (M+H), Rt = 0.50 minutos.

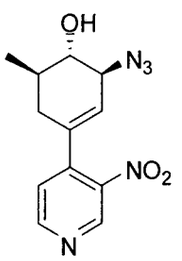
Síntesis de (+/-)-6-bromo-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol



A una solución de la 4-(5-metil-ciclohexa-1,3-dienil)-3-nitro-piridina (1.0 equivalentes) en tetrahidrofurano y agua (1:1, 0.13 M), se le agregó NBS (1.5 equivalentes), y la reacción se agitó a temperatura ambiente durante 30 minutos. Al completarse, se agregaron a la reacción acetato de etilo y agua, la fase orgánica se secó con salmuera, luego con sulfato de sodio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para dar el (+/-)-6-bromo-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol como un aceite

amarillo en un 80 por ciento de rendimiento. LC/MS = 315.0/313.0 (M+H), LC = 2.966 minutos.

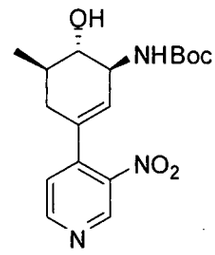
Síntesis de (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol



A una solución del (+/-)-6-bromo-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en tetrahidrofurano (0.1 M), se le agregó terbutóxido de potasio (1.5 equivalentes). La reacción se convirtió desde un color naranja hasta negro casi inmediatamente. Mediante TLC, y la formación del producto es limpia en 30 minutos. Se apagó mediante la adición de cloruro de amonio saturado y acetato de etilo. La fase orgánica se secó con salmuera, entonces sulfato de sodio, se filtró, y se concentró. El producto crudo se disolvió en etanol y agua (3:1, 0.1 M), y se agregaron cloruro de amonio (2.0 equivalentes), y azida de sodio (2.0 equivalentes). La reacción color naranja oscuro se agitó a temperatura ambiente durante la noche. La conversión hasta el producto es limpia, como se indica mediante la LC/MS. La reacción se concentró para remover el etanol, se agregaron acetato de etilo y agua, y la fase orgánica

se secó con sulfato de sodio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para dar el (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol en un 55 por ciento de rendimiento. LC/MS = 276.0 (M+H), LC = 2.803 minutos.

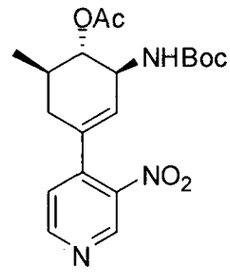
Síntesis de (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo



A una solución del (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol (1.0 equivalentes) en piridina e hidróxido de amonio (8:1, 0.08 M), se le agregó trimetil-fosfina (3.0 equivalentes), y la solución color café se agitó a temperatura ambiente durante 2 horas. Al completarse, se agregó EtOH, y la solución se concentró al vacío. Se agregó más etanol, y la reacción se concentró nuevamente. Al producto crudo se le agregaron dioxano y $NaHCO_3$ saturado (1:1, 0.08 M), seguidos por Boc_2O (1.0 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, y entonces se agregaron agua y acetato de etilo. La fase orgánica se secó con $MgSO_4$, y

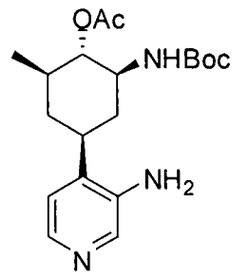
se concentró. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para proporcionar el (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (59 por ciento). LC/MS = 350.1 (M+H), Rt: 0.76 minutos.

Síntesis de (+/-)-acetato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



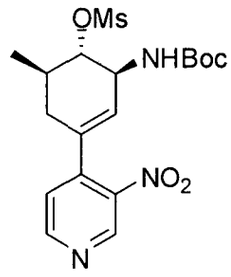
A una solución del (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) en piridina (0.1 M), se le agregó Ac_2O (2.0 equivalentes), y la reacción se agitó a temperatura ambiente durante la noche. Al completarse, la reacción se concentró a sequedad, entonces se procesó con acetato de etilo y agua. La fase orgánica se secó con salmuera, luego con sulfato de sodio, se filtró, y se concentró, para dar el (+/-)-acetato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo en un 94 por ciento de rendimiento. LC/MS = 392.2 (M+H), Rt = 0.94 minutos.

Síntesis de (+/-)-acetato de 4-(3-amino-piridin-4-il)-2-(ter-butoxi-carbonil-amino)-6-metil-ciclohexilo



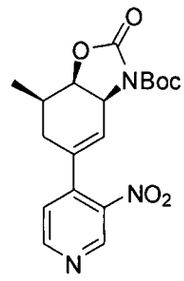
A una solución desgasificada del (+/-)-acetato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en metanol y EtOAc (1:1, 0.1 M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes), y la reacción se agitó a temperatura ambiente bajo un globo de hidrógeno durante 3 días. Al completarse, la solución se filtró a través de una almohadilla de Celite, el almohadilla se lavó con acetato de etilo, y el filtrado se concentró. El material crudo contenía aproximadamente el 10 por ciento del isómero indeseado. El producto crudo se disolvió en acetato de etilo (aproximadamente el 20 por ciento), y hexanos, y se calentó hasta que se disolvió todo. La solución se dejó asentar a temperatura ambiente durante 2 días. El precipitado se recolectó entonces para dar el (+/-)-acetato de 4-(3-amino-piridin-4-il)-2-(ter-butoxi-carbonil-amino)-6-metil-ciclohexilo como el producto puro en un 59 por ciento de rendimiento. LC/MS = 364.3 (M+H), Rt = 0.63 minutos.

Síntesis de metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



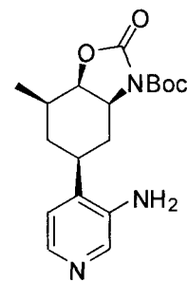
A una solución del 6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de ter-butilo (1.0 equivalentes) en dicloro-metano (0.09 M), se le agregó trietil-amina (1.5 equivalentes), y la reacción se enfrió a 0°C. Se agregó MsCl (1.2 equivalentes) a la reacción, y se agitó durante 3 horas. Se agregó otro 1.0 equivalente de MsCl a la reacción, y se agitó durante otras 2 horas. La reacción se procesó mediante la adición de agua, la fase orgánica se secó con salmuera, sulfato de sodio, y se concentró. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:1), para proporcionar el metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo como una espuma blanca en un 65 por ciento de rendimiento. LC/MS = 428.2 (M+H), LC: 3.542 minutos.

Síntesis de (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



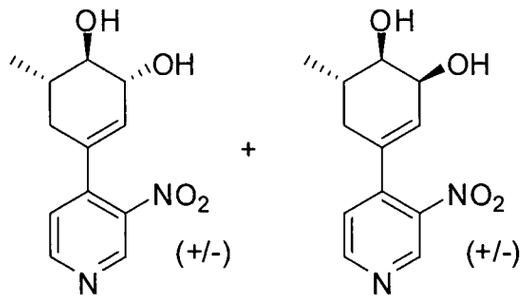
Una solución del (+/-)-metan-sulfonato de 2-(ter-butoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en piridina (0.2 M), se calentó en el reactor de microondas a 110°C durante 10 minutos. La mezcla de reacción color naranja se concentró entonces al vacío, el producto crudo se disolvió en acetato de etilo y agua, la fase orgánica se secó con sulfato de sodio, y se concentró al vacío. El material crudo se disolvió en dicloro-metano (0.2 M), se agregó trietil-amina (1.8 equivalentes), seguida por Boc_2O (1.2 equivalentes). La reacción se agitó durante 40 minutos, y entonces se concentró a sequedad. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con hexano y acetato de etilo (1:1), para proporcionar el (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo como una espuma blanca en un 66 por ciento de rendimiento. LC/MS = 376.0 (M+H), LC: 3.424 minutos.

Síntesis de (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



A una solución desgasificada del (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (1.0 equivalentes) en metanol y EtOAc (1:1, 0.1 M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La reacción se agitó bajo un globo de hidrógeno durante la noche. Al completarse, la solución se filtró a través de una almohadilla de Celite, y la almohadilla se lavó con acetato de etilo. El filtrado se concentró al vacío, para dar el (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo como el producto deseado, como una espuma amarilla en un 93 por ciento de rendimiento. LC/MS = 348.1 (M+H), Rt = 055 minutos.

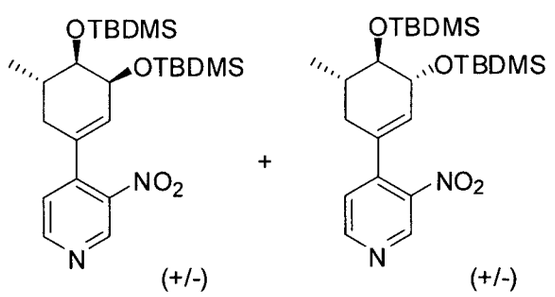
Síntesis de ((+/-)-(1R,2R,6S)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-eno-1,2-diol, y (+/-)-(1R,2S,6S)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-eno-1,2-diol



A una solución del (+/-)-(1S,5S,6S)-6-bromo-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en tetrahidrofurano (0.1M), se le agregó terbutóxido de potasio (1.5 equivalentes), a temperatura ambiente. La mezcla de reacción se agitó durante 10 minutos. La mezcla de reacción se apagó con una solución de NH_4Cl, y se procesó con EtOAc mediante lavado con agua y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró, y se secó al vacío. El producto crudo se utilizó para el siguiente paso sin mayor purificación. R_f = 0.5 (50 por ciento de EtOAc/Hexanos). LCMS: MH+ 251.2 (como un diol), R_t =0.49 minutos. A una solución de la (+/-)-4-((1S,5S)-5-metil-7-oxabiciclo-[4.1.0]-hept-2-en-3-il)-3-nitro-piridina cruda (1.0 equivalentes) en 2:1 de CH_3CN/H_2O (0.1 M), se le agregó ácido acético (0.3 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó durante 16 horas a temperatura ambiente. Después de que se apagó con una solución de $NaHCO_3$, la mezcla de

reacción se concentró para remover la mayor parte del CH_3CN, y el residuo se dividió entre EtOAc y agua. La capa orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró al vacío. Se obtuvo una mezcla de los dioles ((+/-)-(1R,2R,6S)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-eno-1,2-diol, y (+/-)-(1R,2S,6S)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-eno-1,2-diol) en un 33.1 por ciento de rendimiento como un sólido blanco mediante cromatografía en columna por evaporación instantánea. R_f = 0.3 (100 por ciento de EtOAc; los dioles no se pudieron separar en la TLC). LCMS: MH+ 251.2, R_t =0.49 minutos.

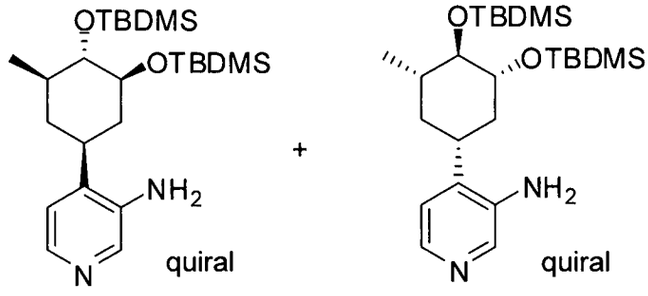
Síntesis de (+/-)-4-((3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina y (+/-)-4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina



A una solución de una mezcla de dioles (1.0 equivalentes) en N,N-dimetil-formamida (0.3 M), se le agregaron TBDMSCl (7.0 equivalentes), e imidazol (9 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura

ambiente durante la noche. Después de que se apagó con $NaHCO_3$ saturado, la mezcla de reacción se extrajo con EtOAc. La capa orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró al vacío. La mezcla se purificó mediante cromatografía en columna de sílice automatizada en secuencia (gradiente eluyendo con EtOAc y hexanos), y HPLC de preparación en fase inversa (del 55 por ciento al 95 por ciento de acetonitrilo en agua, y luego se ejecutó con del 5 por ciento al 95 por ciento de acetonitrilo en agua), para proporcionar la (+/-)-4-((3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (27.2 por ciento), y la (+/-)-4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (50.2 por ciento). LCMS: MH+ 479.2, R_t =1.60 y 1.63 minutos.

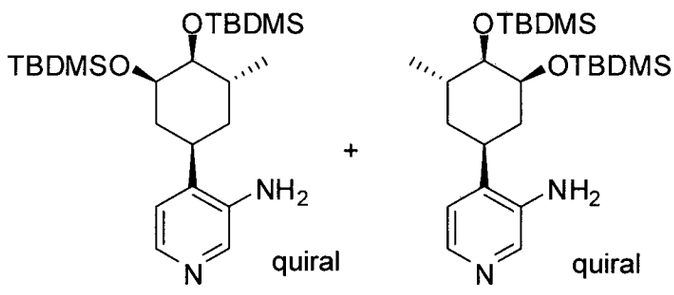
Síntesis de 4-((1S,3S,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina y de 4-((1R,3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina



A una solución de la (+/-)-4-((3R,4R,5S)-3,4-bis-(ter-butil-

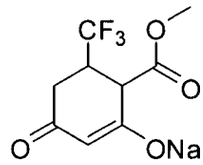
dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) en etanol/EtOAc, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con EtOAc. Los volátiles se removieron al vacío, y el material crudo se purificó mediante cromatografía en columna de sílice automatizada (R_f = 0.2, EtOAc al 40 por ciento en Heptano), para proporcionar el producto racémico puro. LCMS: MH+ 451.3, Rt =1.35 minutos. El compuesto racémico se resolvió mediante cromatografía quiral (columna IC, 1 mililitro/minuto, ácido isopropílico al 5 por ciento en heptano), para proporcionar la 4-((1S,3S,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina (6.01 minutos), y la 4-((1R,3R,4R, 5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina (8.34 minutos).

<u>Síntesis de 4-((1R,3R,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina y de 4-((1S,3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina</u>



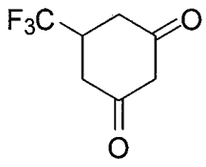
A una solución de la (+/-)-4-((3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) en etanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con etanol. Los volátiles se removieron al vacío, y el material crudo se purificó mediante cromatografía en columna de sílice automatizada (R_f = 0.2, EtOAc al 40 por ciento en heptano), para proporcionar el producto racémico puro (50.4 por ciento). LCMS: MH+ 451.3, R_t =1.35 minutos. El compuesto racémico se resolvió mediante cromatografía quiral (columna IC, 1 mililitro/minuto, ácido isopropílico al 5 por ciento en heptano), para proporcionar la 4-((1R,3R,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina (6.98 minutos), y la 4-((1S,3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina (8.67 minutos).

Síntesis de 6-(metoxi-carbonil)-3-oxo-5-(trifluoro-metil)-ciclohex-1-enolato de sodio



A una solución recién preparada de sodio (1.0 equivalentes) en t-BuOH (1 M), se le agregó aceto-acetato de etilo (1.0 equivalentes) por goteo, y la mezcla se agitó sobre un baño de hielo durante 15 minutos adicionales. Se agregó por goteo 4,4,4-trifluoro-crotonato de etilo (1.0 equivalentes), y la mezcla se agitó a temperatura ambiente durante 30 minutos adicionales. Después de poner a reflujo durante 2 horas, la mezcla se enfrió y se agregaron hexanos. El precipitado se filtró sin mayor purificación, para dar el 6-(metoxi-carbonil)-3-oxo-5-(trifluoro-metil)-ciclohex-1-enolato de sodio (46 por ciento). LC/MS (*m/z*): MH^+ = 253.1, Rt = 0.70 minutos.

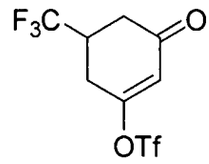
Síntesis de 5-(trifluoro-metil)-ciclohexano-1,3-diona



El 6-(metoxi-carbonil)-3-oxo-5-(trifluoro-metil)-ciclohex-1-enolato de sodio (1.0 equivalentes) se disolvió en NaOH 1M (1.0 equivalentes), y la mezcla se puso a reflujo durante 1 hora. Después de enfriar a temperatura ambiente, la mezcla se acidificó con ácido sulfúrico 5 M. La mezcla se extrajo con EtOAc. Después de lavar con agua, la capa orgánica se secó sobre sulfato de magnesio, y el solvente se removió bajo presión reducida, para dar la 5-(trifluoro-metil)-ciclohexano-

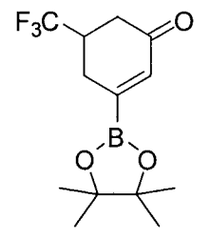
1,3-diona, la cual se utilizó para el siguiente paso sin mayor purificación (98 por ciento). LC/MS (*m/z*): MH^+ =181.1, Rt = 0.55 minutos.

Síntesis de trifluoro-metan-sulfonato de 3-oxo-5-(trifluoro-metil)-ciclohex-1-enilo



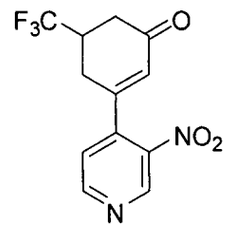
A una suspensión de la 5-(trifluoro-metil)-ciclohexano-1,3-diona (1.0 equivalentes) en dicloro-metano (0.23 M), se le agregó trietil-amina (1.2 equivalentes), para dar una solución transparente. La mezcla se enfrió a 0°C. y entonces se agregó por goteo Tf_2O (1.05 equivalentes) en dicloro-metano. La mezcla de reacción se agitó a esa temperatura durante 2 horas. La mezcla de reacción se diluyó con dicloro-metano, y se lavó con agua, $NaHCO_3$ acuoso, salmuera, y se secó sobre $MgSO_4$, se filtró, y se concentró, para dar el trifluoro-metan-sulfonato de 3-oxo-5-(trifluoro-metil)-ciclohex-1-enilo, el cual se utilizó para el siguiente paso directamente. LC/MS (*m/z*): MH^+ = 313.0, Rt = 1.02 minutos.

Síntesis de 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5-(trifluoro-metil)-ciclohex-2-enona



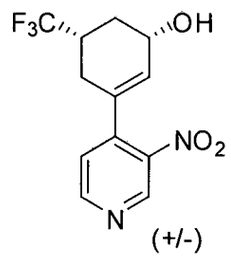
Todos los reactivos en trifluoro-metan-sulfonato de 3-oxo-5-(trifluoro-metil)-ciclohex-1-enilo (1.0 equivalentes), NaOAc (3.0 equivalentes), y bis-(pinacolato)-diboro (2.0 equivalentes) se agregaron a 1,4-dioxano (0.23 M) en un matraz de fondo redondo, y se desgasificaron mediante burbujeo de N_2 a través de la mezcla durante 10 minutos. Se agregó el aducto de $PdCl_2(dppf).CH_2Cl_2$ (0.1 equivalentes), y la reacción se calentó a 80°C adaptándose con un condensador de reflujo sobre un baño de aceite bajo N_2 durante dos horas. La mezcla se enfrió a temperatura ambiente, se filtró a través de un embudo de vidrio de frita grueso, y la torta se enjuagó con aproximadamente 10 mililitros de 1,4-dioxano, para dar la 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5-(trifluoro-metil)-ciclohex-2-enona en 1,4-dioxano, la cual se utilizó para el siguiente paso directamente. LC/MS (*m/z*): MH^+ = 209.1 (ácido borónico), Rt=0.60 minutos.

Síntesis de 3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enona



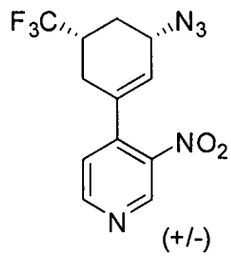
El éster de boronato de la 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5-(trifluoro-metil)-ciclohex-2-enona (1.0 equivalentes) se disolvió en 1,4-dioxano (0.14 M) en un matraz de fondo redondo que se desgasificó mediante burbujeo de N_2 a través de la solución durante 30 minutos. Se agregaron 4-cloro-3-nitro-piridina (1.3 equivalentes), y Na_2CO_3 acuoso (2M, 2.0 equivalentes), y se burbujeó N_2 a través de los mismos de durante 10 minutos, y luego se agregó el aducto de $PdCl_2(dppf).CH_2Cl_2$ (0.1 equivalentes). La mezcla de reacción se agitó a 100°C durante 2 horas. A la mezcla se le agregaron EtOAc y salmuera. La mezcla resultante se filtró a través de Celite, y la torta se lavó con EtOAc. La capa orgánica se separó y se lavó con salmuera, se secó sobre $MgSO_4$, y se filtró y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (eluida con EtOAc:Hexanos = de 1:10 a 2:1), para dar la 3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enona (73 por ciento en tres pasos a partir de la dicetona). LC/MS (*m/z*): MH^+ = 287.1, Rt = 0.85 minutos.

Síntesis de cis-3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enol



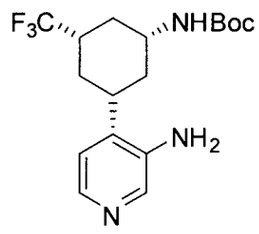
La 3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enona (1.0 equivalentes) se mezcló con heptahidrato de cloruro de cerio (III) (1.0 equivalentes), y se agregó etanol absoluto (0.17). La mezcla se agitó a temperatura ambiente hasta que se disolvieron todos los sólidos. La mezcla se enfrió sobre un baño de hielo, y se agregó $NaBH_4$ (1.2 equivalentes) en porciones. La reacción se agitó sobre el baño de hielo durante 1 hora. La mezcla se diluyó con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (1:1 de acetato de etilo y hexanos), para dar el cis-3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enol (66 por ciento). LC/MS (*m/z*): MH^+ = 289.2, Rt = 0.72 minutos.

Síntesis de cis-4-(3-azido-5-(trifluoro-metil)-ciclohex-1-enil)-3-nitro-piridina



A una solución del cis-3-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-ciclohex-2-enol (1.0 equivalentes) en dicloro-metano (0.14 M), se le agregó trietil-amina (2.5 equivalentes), seguida por MsCl (1.8 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El solvente se removió. El residuo se disolvió en N,N-dimetil-formamida (0.19 M), y entonces a la mezcla se le agregó azida de sodio (1.2 equivalentes). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. Se agregaron otros 1.2 equivalentes de azida de sodio. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo y heptano, y se lavó con NaCl saturado. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante columna (1:1 de acetato de etilo y hexanos), para dar la cis-4-(3-azido-5-(trifluoro-metil)-ciclohex-1-enil)-3-nitro-piridina (58 por ciento). LC/MS (*m/z*): MH^+ = 314.1, Rt = 0.96 minutos.

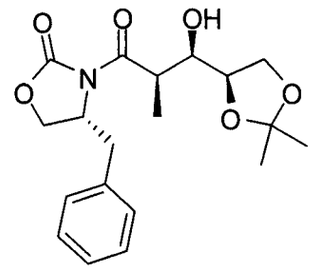
Síntesis de (1R,3R,5S)-3-(3-amino-piridin-4-il)-5-(trifluoro-metil)-ciclohexil-carbamato de ter-butilo



Una solución de la cis-4-(3-azido-5-(trifluoro-metil)-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) en etanol (0.13 M) se burbujeó con N_2 durante 20 minutos. Entonces a la mezcla de reacción se le agregaron anhídrido de Boc (1.5 equivalentes), y Pd/C (0.2 equivalentes). La mezcla de reacción se agitó a temperatura ambiente bajo una atmósfera de H_2 durante la noche. El sólido se removió mediante filtración sobre Celite, y se enjuagó con EtOH. El residuo se purificó mediante columna (metanol al 5 por ciento en 1:1 de acetato de etilo y hexanos), para dar el cis-3-(3-amino-piridin-4-il)-5-(trifluoro-metil)-ciclohexil-carbamato racémico (57 por ciento). LC/MS (m/z): MH+ = 360.2, Rt = 0.72 minutos. Se resolvieron el (1R,3R,5S)-3-(3-amino-piridin-4-il)-5-(trifluoro-metil)-ciclohexil-carbamato de ter-butilo enantioméricamente puro y la N-(4-((1S,3S,5R)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida mediante HPLC quiral (para el análisis, R_t = 8.14 minutos y 10.59 minutos, respectivamente; heptano:isopropanol = 90:10 (volumen:volumen), Chiralcel IC de 100 x 4.6 milímetros a 1

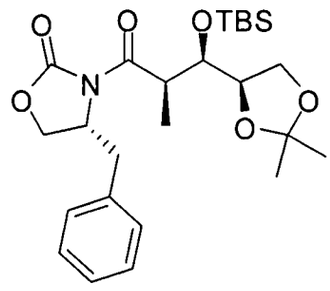
mililitro/minuto. Para la separación de preparación, se utilizó heptano:isopropanol = 90:10 (volumen:volumen), Chiralcel IC de 250 x 20 milímetros a 15 mililitros/minuto).

Síntesis de (R)-4-bencil-3-((2R,3R)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-3-hidroxi-2-metil-propanoil)-oxazolidin-2-ona



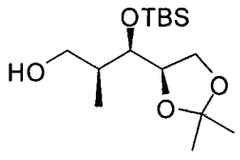
La (R)-4-bencil-3-((2R,3R)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-3-hidroxi-2-metil-propanoil)-oxazolidin-2-ona se preparó de la manera reportada (Proc. Nat. Acad. Sciences, 101, 33, 2004, páginas 12042-12047) para el compuesto enantiomérico empezando con la (R)-4-bencil-3-propionil-oxazolidin-2-ona y el acetoniuro de R-gliceraldehído.

Síntesis de (R)-4-bencil-3-((2R,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propanoil)-oxazolidin-2-ona



La (R)-4-bencil-3-((2R,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propanoil)-oxazolidin-2-ona se preparó de la manera reportada (Proc. Nat. Acad. Sciences, 101, 33, 2004, páginas 12042-12047) para el compuesto enantiomérico empezando con la (R)-4-bencil-3-((2R,3R)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-3-hidroxi-2-metil-propanoil)-oxazolidin-2-ona.

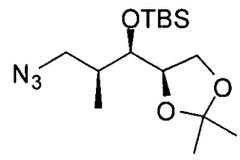
Síntesis de (2S,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propan-1-ol



A una solución de la (R)-4-bencil-3-((2R,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propanoil)-oxazolidin-2-ona (1.0 equivalentes), y etanol (3.0 equivalentes) en tetrahidrofurano (0.09 M), se le agregó $LiBH_4$ (1.0 equivalentes) a -40°C. La mezcla de reacción se dejó calentar hasta la temperatura ambiente lentamente, y se agitó a esa temperatura durante 12 horas. La solución se enfrió de regreso hasta -40°C, y se agregó $LiBH_4$ adicional (0.3 equivalentes). Después de calentar de regreso hasta la temperatura ambiente y de agitar durante 2 horas, la solución se diluyó entonces con dietil-éter, y se le agregó NaOH 1N. La mezcla resultante se extrajo con acetato de etilo, la capa

orgánica se separó, se lavó con NaCl (saturado), se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice (del 10 al 30 por ciento de EtOAc/n-heptanos), proporcionando el (2S,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propan-1-ol (75 por ciento). LC/MS = 247.1 (M+H-cetal-H_2O), R_t = 0.64 minutos.

Síntesis de ((1R,2S)-3-azido-1-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propoxi)-(ter-butil)-dimetil-silano

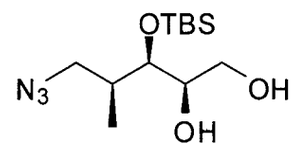


A una solución del (2S,3R)-3-(ter-butil-dimetil-sililoxi)-3-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propan-1-ol (1.0 equivalentes), DIAD (2.0 equivalentes), y PPh_3 (2.0 equivalentes) en tetrahidrofurano (0.18 M), se le agregó DPPA (1.0 equivalente, solución 1M en tetrahidrofurano). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de la remoción de los volátiles al vacío, el residuo se purificó mediante cromatografía en columna de gel de sílice (2-3-5 por ciento de EtOAc/n-heptanos), proporcionando el ((1R,2S)-3-azido-1-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propoxi)-(ter-butil)-dimetil-silano (62 por ciento).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 4.04-4.10 (m, 1H), 3.94 (dd,

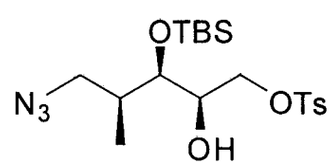
J=8.0, 6.4, 1H), 3.72 (d, J=7.2, 1H), 3.53 (t, J=8.0, 1H), 3.36 (dd, J=12, 8.0, 1H), 3.19 (dd, J=12.0, 6.7, 1H), 1.52-1.60 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 0.92 (d, J=7.2, 3H), 0.90 (s, 9 H), 0.12 (s, 3H), 0.09 (s, 3H).

Síntesis de (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-4-metil-pentano-1,2-diol



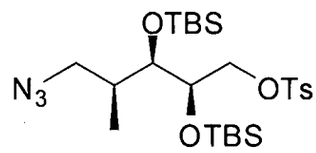
A una solución del ((1R,2S)-3-azido-1-((R)-2,2-dimetil-1,3-dioxolan-4-il)-2-metil-propoxi)-(ter-butil)-dimetil-silano (1.0 equivalentes) en metanol (0.1 M), se le agregó PPTS (1.0 equivalentes), y la mezcla se agitó a temperatura ambiente durante 14 horas, a 50°C durante 2 horas, y a 80°C durante 1 hora. Los volátiles se removieron al vacío, y el residuo se purificó mediante cromatografía en columna de gel de sílice (del 10 al 25 por ciento de EtOAc/n-heptanos), proporcionando el (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-4-metil-pentano-1,2-diol (40 por ciento).

Síntesis de (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-3-(ter-butil-dimetil-sililoxi)-2-hidroxi-4-metil-pentilo



A una solución del (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-1-hidroxi-4-metil-pentan-2-il-carbamato de ter-butilo (1.0 equivalentes) en piridina (0.2 M), se le agregó pTsCl (1.3 equivalentes) a 0°C. La mezcla se mantuvo a esta temperatura durante 16 horas. Los volátiles se removieron al vacío, y el residuo se purificó mediante cromatografía en columna de gel de sílice (10-15-20 por ciento de EtOAc/n-heptanos), proporcionando el (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-3-(ter-butil-dimetil-sililoxi)-2-hidroxi-4-metil-pentilo.

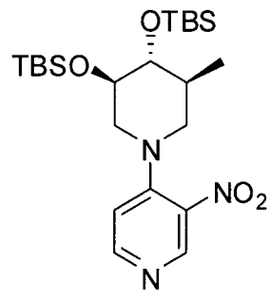
Síntesis de (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-2,3-bis-(ter-butil-dimetil-sililoxi)-4-metil-pentilo



A una solución del (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-3-(ter-butil-dimetil-sililoxi)-2-hidroxi-4-metil-pentilo (1.0 equivalentes), y 2,6-lutidina (3.4 equivalentes), se le agregó TBDMSOTf (1.7 equivalentes) a 0°C. La solución se agitó durante 7 horas a medida que se calentaba hasta la temperatura ambiente. La solución se diluyó con EtOAc, se lavó con $CuSO_4$ al 10 por ciento, H_2O, Na_2CO_3 (saturado), NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice (2.5-5-10-20 por ciento de EtOAc/n-heptanos),

proporcionando el (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-2,3-bis-(ter-butil-dimetil-sililoxi)-4-metil-pentilo (75 por ciento).

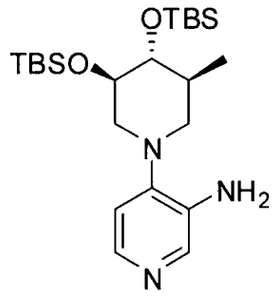
Síntesis de 4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-1-il)-3-nitro-piridina



Una solución del (2R,3R,4S)-4-metil-bencen-sulfonato de 5-azido-2,3-bis-(ter-butil-dimetil-sililoxi)-4-metil-pentilo en EtOH (0.05 M) se desgasificó con argón. Se agregó DIEA (1.5 equivalentes), seguida por Pd/C al 10 por ciento (0.1 equivalentes). La mezcla de reacción se agitó bajo un globo de hidrógeno durante 3 horas. La solución se desgasificó y se purgó con argón, en cuyo tiempo se agregaron 4-cloro-3-nitro-piridina (1.5 equivalentes), y DIEA adicional (1.5 equivalentes). Después de agitar a temperatura ambiente durante 15 horas, la solución se filtró para remover el Pd/C y los volátiles se removieron al vacío. El residuo se diluyó con acetato de etilo, y se lavó con Na_2CO_3 (saturado), NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice (del 10 al

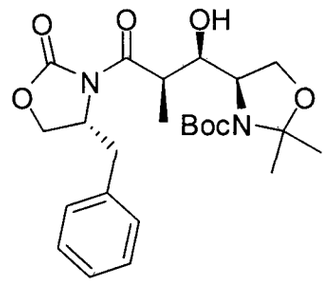
15 por ciento de EtOAc/n-heptanos), proporcionando la 4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-1-il)-3-nitro-piridina (40 por ciento). LC/MS = 482.4 (M+H), R_t = 1.26 minutos.

Síntesis de 4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-1-il)-piridin-3-amina



A una solución de la 4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-1-il)-3-nitro-piridina (1.0 equivalentes) en etanol, en una concentración de 0.05 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con etanol. Los volátiles se removieron al vacío, proporcionando la 4-((3R,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-1-il)-piridin-3-amina. LC/MS = 452.4 (M+H), R_t = 1.31 minutos.

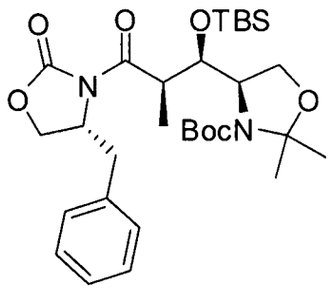
Síntesis de (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-hidroxi-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo



A una solución de la (R)-4-bencil-3-propionil-oxazolidin-2-ona (1.0 equivalentes) en dicloro-metano (0.13 M), se le agregó $TiCl_4$ (1.0 equivalentes) a -40°C. La mezcla se agitó a -40°C durante 10 minutos (suspensión amarilla), entonces se agregó di-isopropil-etil-amina (2.5 equivalentes), (solución color rojo oscuro), y se agitó a 0°C durante 20 minutos. Luego se agregó por goteo el (R)-4-formil-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo (1.0 equivalentes) en dicloro-metano (0.5 M), y la mezcla resultante se agitó durante 1.5 horas. La reacción se apagó mediante la adición de cloruro de amonio acuoso, y la mezcla se extrajo con acetato de etilo. La fase orgánica se separó, se lavó con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna, eluyendo con acetato de etilo y hexanos (1:4), para dar el (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-hidroxi-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo como el producto mayor

(5:2) en un 58 por ciento de rendimiento. LC/MS = 363.3 (M+H-Boc), Rt = 1.09 minutos.

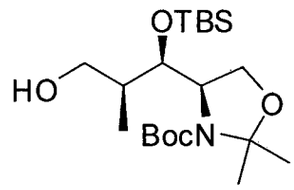
Síntesis de (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-(ter-butil-dimetil-sililoxi)-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo



A una solución del (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-hidroxi-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo (1.0 equivalentes), y lutidina (1.8 equivalentes) en dicloro-metano (0.1M), se le agregó TBSOTf (1.4 equivalentes) a -40°C. La mezcla de reacción se agitó a -40°C durante 2 horas. La solución se diluyó con acetato de etilo, y se lavó con $NaHCO_3$ saturado, NaCl saturado, se secó con sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:4), para dar el (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-(ter-butil-dimetil-sililoxi)-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo como el producto mayor (5:2) en un 83 por ciento de rendimiento.

LC/MS = 577.3 (M+H), Rt = 1.33 minutos (método de fraccionamiento del 65 por ciento al 95 por ciento).

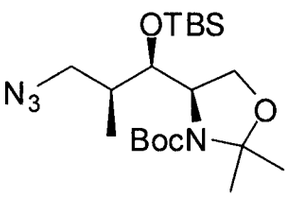
Síntesis de (R)-4-((1R,2S)-1-(ter-butil-dimetil-sililoxi)-3-hidroxi-2-metil-propil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo



A una solución del (R)-4-((1R,2R)-3-((R)-4-bencil-2-oxo-oxazolidin-3-il)-1-(ter-butil-dimetil-sililoxi)-2-metil-3-oxopropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo (1.0 equivalentes), y etanol (3.0 equivalentes) en tetrahidrofurano (0.09 M), se le agregó $LiBH_4$ (3.0 equivalentes) a -30°C. La mezcla de reacción se dejó calentar hasta 0°C, y se agitó a esa temperatura durante 3 horas. La solución se diluyó entonces con dietil-éter, y se le agregó NaOH 1N. La mezcla resultante se extrajo con acetato de etilo, la capa orgánica se separó, se lavó con NaCl saturado, se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:4), para dar el (R)-4-((1R,2S)-1-(ter-butil-dimetil-sililoxi)-3-hidroxi-2-metil-propil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo como el producto mayor (5:2 ratio) en un 71 por ciento de rendimiento. LC/MS = 304.3

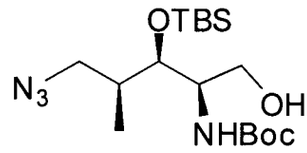
(M+H-Boc), Rt = 0.95 minutos (método de fraccionamiento del 65 por ciento al 95 por ciento).

Síntesis de (R)-4-((1R,2S)-3-azido-1-(ter-butil-dimetil-sililoxi)-2-metil-propil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo



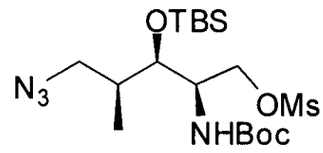
A una solución del (R)-4-((1R,2S)-1-(ter-butil-dimetil-sililoxi)-3-hidroxi-2-metilpropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo (1.0 equivalentes), DIAD (2.0 equivalentes), y PPh_3 (2.0 equivalentes) en tetrahidrofurano (0.18 M), se le agregó DPPA (2.0 equivalentes, solución 1M en tetrahidrofurano). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de la remoción de los volátiles al vacío, el residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:6), para dar el (R)-4-((1R,2S)-3-azido-1-(ter-butil-dimetil-sililoxi)-2-metil-propil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo como el producto mayor (5:2) en un 86 por ciento de rendimiento. LC/MS = 329.3 (M+H-Boc), Rt = 1.40 minutos (método de fraccionamiento del 65 por ciento al 95 por ciento).

Síntesis de (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-1-hidroxi-4-metil-pentan-2-il-carbamato de ter-butilo



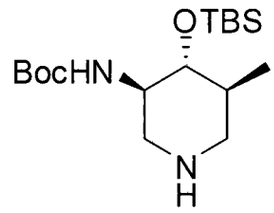
A una solución del (R)-4-((1R,2S)-3-azido-1-(ter-butil-dimetil-sililoxi)-2-metilpropil)-2,2-dimetil-oxazolidin-3-carboxilato de ter-butilo (1.0 equivalentes) en EtOH (0.1 M), se le agregó PPTS (1.3 equivalentes), y la mezcla se puso a reflujo durante 2 días. Los volátiles se removieron al vacío, el residuo se disolvió en dicloro-metano (0.1 M), y se agregaron DIEA (1.5 equivalentes) y Boc_2O (1.0 equivalentes) a la mezcla de reacción. La solución se agitó durante 3 horas a temperatura ambiente. Los solventes se removieron bajo presión reducida, y el residuo se diluyó con acetato de etilo, se lavó con agua, $NaHSO_4$ acuoso, $NaHCO_3$ acuoso, NaCl saturado, la fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:3), para dar el (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-1-hidroxi-4-metil-pentan-2-il-carbamato de ter-butilo como el isómero mayor (5:2) en un 70 por ciento de rendimiento. LC/MS = 289.3 (M+H-Boc), Rt = 0.76 minutos (método de fraccionamiento del 65 por ciento al 95 por ciento).

Síntesis de (2R,3R,4S)-metan-sulfonato de 5-azido-2-(ter-butoxi-carbonil-amino)-3-(ter-butil-dimetil-sililoxi)-4-metil-pentilo



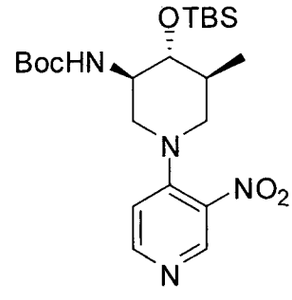
A una solución del (2R,3R,4S)-5-azido-3-(ter-butil-dimetil-sililoxi)-1-hidroxi-4-metil-pentan-2-il-carbamato de ter-butilo (1.0 equivalentes) en piridina (0.2 M), se le agregó MsCl (1.3 equivalentes), seguido por DMAP (cantidad catalítica) a 0°C. La mezcla se agitó a esa temperatura durante 1 hora. La solución se diluyó con éter y acetato de etilo (4:1), se lavó con $NaHSO_4$ acuoso, $NaHCO_3$ saturado, salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:3), para dar el (2R,3R,4S)-metan-sulfonato de 5-azido-2-(ter-butoxi-carbonil-amino)-3-(ter-butil-dimetil-sililoxi)-4-metil-pentilo como el isómero mayor (5:2) en un 90 por ciento de rendimiento. LC/MS = 367.3 (M+H-Boc), Rt = 0.81 minutos (método de fraccionamiento del 65 por ciento al 95 por ciento).

Síntesis de (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-3-il-carbamato de ter-butilo



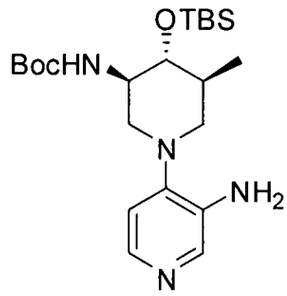
Una solución del (2R,3R,4S)-metan-sulfonato de 5-azido-2-(ter-butoxi-carbonil-amino)-3-(ter-butil-dimetil-sililoxi)-4-metil-pentilo en metanol (0.09 M) se desgasificó con nitrógeno durante 20 minutos. Se agregó DIEA (2.5 equivalentes), seguida por Pd/C al 10 por ciento (0.1 equivalentes). La mezcla de reacción se agitó bajo un globo de hidrógeno durante 2 horas. La solución se filtró, y el filtrado se concentró al vacío, para proporcionar el (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-3-il-carbamato de ter-butilo como el isómero mayor (5:2) en >99 por ciento de rendimiento. LC/MS = 345.2 (M+H-Boc), Rt = 0.95 y 0.99 minutos.

Síntesis de (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de ter-butilo



A una solución del (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-3-il-carbamato de ter-butilo (1.0 equivalentes) en i-PrOH (0.09 M), se le agregaron DIEA (2.5 equivalentes), y 4-cloro-3-nitro-piridina (1.5 equivalentes). La mezcla de reacción se agitó a 60°C durante 2 horas. Los volátiles se removieron al vacío, el residuo se diluyó con acetato de etilo, y se lavó con NaCl saturado. La fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:2), para dar el (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de ter-butilo en un 76 por ciento de rendimiento. LC/MS = 467.3 (M+H), Rt = 1.09 minutos.

Síntesis de (3R,4R,5S)-1-(3-amino-piridin-4-il)-4-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-3-il-carbamato de ter-butilo

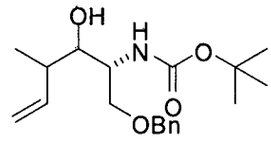


Una solución del (3R,4R,5S)-4-(ter-butil-dimetil-sililoxi)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de ter-butilo (1.0 equivalentes) en metanol (0.05 M) se desgasificó con nitrógeno durante 20 minutos. A la mezcla se le agregó

Pd/C al 10 por ciento (0.2 equivalentes), y la solución se agitó bajo un globo de hidrógeno durante 3 horas. La reacción se filtró, y el filtrado se concentró bajo presión reducida, para dar el (3R,4R,5S)-1-(3-amino-piridin-4-il)-4-(ter-butil-dimetil-sililoxi)-5-metil-piperidin-3-il-carbamato de ter-butilo como el producto deseado en un 94 por ciento de rendimiento. LC/MS = 437.4 (M+H), Rt = 1.08 minutos.

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.95 (d, J = 6.0 Hz, 1H), 6.76 (d, J = 6.0 Hz, 1H), 4.44 (br s, 1H), 3.74 (br s, 2H), 3.59-3.55 (m, 1H), 3.25-3.13 (m, 2H), 2.47-2.35 (m, 2H), 1.89 (br s, 2H), 1.44 (s, 9H), 1.04 (d, J = 6.0, 3H), 0.92 (s, 9H), 0.13 (d, J = 9.0, 6H).

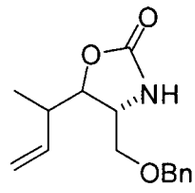
Síntesis de (2R)-1-(benciloxi)-3-hidroxi-4-metil-hex-5-en-2-il-carbamato de ter-butilo



A una solución de N-Boc, O-bencil-D-Serina-aldehído (1.0 equivalentes) en dicloro-metano (0.1 M) a -78°C bajo una atmósfera de argón, se le agregó (Z)-2-(but-2-enil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (1.1 equivalentes), y la solución transparente se agitó durante 16 horas a medida que se calentaba a temperatura ambiente. La solución se agregó a EtOAc, y se lavó con H_2O (3 veces) y NaCl saturado, se secó

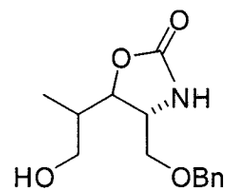
sobre $MgSO_4$ y se purificó mediante cromatografía en gel de sílice (15 por ciento de EtOAc/hexanos), para proporcionar el (2R)-1-(benciloxi)-3-hidroxi-4-metil-hex-5-en-2-il-carbamato de ter-butilo (54 por ciento) como una mezcla de isómeros, 3:1, como fue juzgado mediante ^1H RMN. LCMS (*m/z*): 236.3 (MH^+-Boc); LC R_t = 4.37 y 4.51 minutos.

Síntesis de (4R)-4-(benciloxi-metil)-5-(but-3-en-2-il)-oxazolidin-2-ona



A una solución de (2R)-1-(benciloxi)-3-hidroxi-4-metil-hex-5-en-2-carbamato de ter-butilo en tetrahidrofurano (0.1 M), se le agregó hidruro de sodio al 60 por ciento en aceite mineral (1.5 equivalentes). Después de agitar durante 3 días, la reacción se apagó mediante la adición de NH_4Cl saturado, y la solución se diluyó con EtOAc, y se lavó con NH_4Cl saturado y NaCl saturado, se secó sobre $MgSO_4$ y se purificó mediante cromatografía en gel de sílice (50 por ciento de EtOAc/hexanos), para proporcionar la (4R)-4-(benciloxi-metil)-5-(but-3-en-2-il)-oxazolidin-2-ona (89 por ciento) como una mezcla 3:1. LCMS (*m/z*): 262.2 (MH^+); LC R_t = 3.47 minutos.

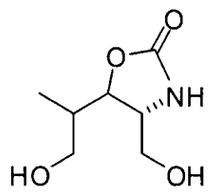
Síntesis de (4R)-4-(benciloxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona



A una solución de la (4R)-4-(benciloxi-metil)-5-(but-3-en-2-il)-oxazolidin-2-ona (1.0 equivalentes) en 2:1 de MeOH / H_2O (0.04 M), se le agregaron tetróxido de osmio al 4 por ciento en H_2O (0.07 equivalentes) y peryodato de sodio (3.0 equivalentes). Después de agitar durante 3 horas, el precipitado blanco se filtró, y se enjuagó con EtOAc. El filtrado combinado se concentró al vacío, y el residuo se disolvió en EtOAc, se lavó con NaCl saturado, se secó sobre $MgSO_4$, se filtró, y se concentró. El aldehído crudo se disolvió en EtOH (0.08 M) y, después de enfriarse a 0°C, se agregó borohidruro de sodio (2.0 equivalentes). Después de agitar durante 15 horas y de llegar a la temperatura ambiente, la reacción se apagó mediante la adición de H_2O. Después de agitar durante 20 minutos, el EtOH se removió al vacío, se agregó EtOAc, y la solución se lavó con HCl 1N, $NaHCO_3$ saturado y NaCl saturado, se secó sobre $MgSO_4$, se filtró, y se concentró, proporcionando, después de la purificación mediante cromatografía en gel de sílice, la (4R)-4-(benciloxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona como una mezcla de

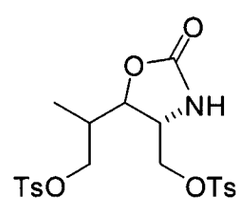
isómeros, 3:1 (60 por ciento). LCMS (*m/z*): 266.1 (MH^+); LC R_t = 2.28 minutos.

Síntesis de (4R)-4-(hidroxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona



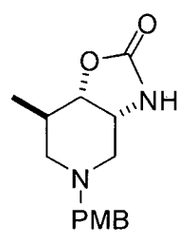
A una solución de la (4R)-4-(benciloxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 15 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la (4R)-4-(hidroxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona (99 por ciento). LCMS (*m/z*): 176.1 (MH^+).

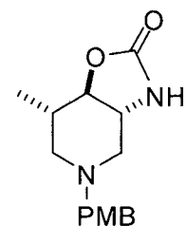
Síntesis de 4-metil-bencen-sulfonato de 2-((4R)-2-oxo-4-(tosiloxi-metil)-oxazolidin-5-il)-propilo



A una solución de la (4R)-4-(hidroxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona (1.0 equivalentes) en piridina (0.15 M) a 0°C, se le agregó cloruro de p-toluen-sulfonilo (2.1 equivalentes). La solución se dejó calentar a temperatura ambiente a medida que se agitaba durante 14 horas, en cuyo tiempo, se agregó EtOAc, y la solución se lavó con H_2O (3 veces), $CuSO_4$ saturado (2 veces), H_2O, Na_2CO_3 saturado, y NaCl saturado, se secó sobre $MgSO_4$, se filtró, se concentró, y se purificó mediante cromatografía en gel de sílice (eluyente del 75 por ciento de EtOAc/hexanos), proporcionando el 4-metil-bencen-sulfonato de 2-((4R)-2-oxo-4-(tosiloxi-metil)-oxazolidin-5-il)-propilo (68 por ciento). LCMS (*m/z*): 484.1 (MH^+); LC R_t = 4.06 minutos.

<u>Síntesis de (3aR,7R,7aS)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona y (3aR,7S,7aR)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona</u>

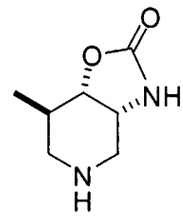




Una solución del 4-metil-bencen-sulfonato de 2-((4R)-2-oxo-4-(tosiloxi-metil)-oxazolidin-5-il)-propilo (1.0 equivalentes), di-isopropil-etil-amina (3.0 equivalentes), y para-metoxi-bencil-

amina (1.5 equivalentes) en NMP (0.05 M) se calentó a 100°C durante 14 horas. La solución se purificó directamente mediante HPLC en fase inversa. Las fracciones del producto se desalaron mediante la adición al EtOAc y al Na_2CO_3 saturado, se lavaron adicionalmente con NaCl saturado, se secaron sobre $MgSO_4$ y se concentraron, proporcionando dos isómeros separados de (3aR,7R,7aS)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona y (3aR,7S,7aR)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (27 por ciento y 8 por ciento). LCMS (*m/z*): 277.2 (MH^+) a los 0.40 y 0.42 minutos.

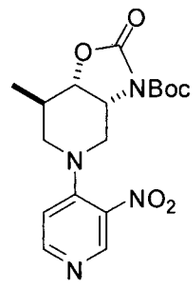
Síntesis de (3aR,7R,7aS)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona



A una solución de la (3aR,7R,7aS)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó hidróxido de paladio al 20 por ciento sobre carbón (0.3 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 2 horas. En este tiempo la mezcla se filtró a través de una almohadilla de

Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la (3aR,7R,7aS)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (99 por ciento). LCMS (*m/z*): 157.1 (MH^+) a los 0.16 minutos.

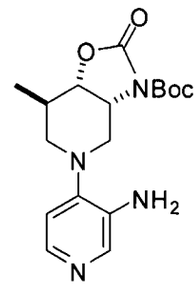
Síntesis de (3aR,7R,7aS)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo



Una solución de 4-cloro-3-nitro-piridina (1.3 equivalentes) y (3aR,7R,7aS)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (1.5 equivalentes) en CH_2Cl_2, en una concentración de 0.1 M, se agitó a temperatura ambiente durante 48 horas, a lo cual se le agregó piperidina (0.4 equivalentes), para consumir el exceso de 4-cloro-3-nitro-piridina. Después de agitar durante 2 horas adicionales, se agregaron dicarbonato de diterbutilo (2.0 equivalentes) y dimetil-amino-piridina (0.1 equivalentes). Después de agitar durante 4 horas, la solución se dividió entre EtOAc y $NaHCO_3$ saturado, se lavó adicionalmente con $NaHCO_3$ saturado y NaCl saturado, se secó sobre $MgSO_4$, se filtró, y se purificó mediante cromatografía en gel de sílice, proporcionando el (3aR,7R,7aS)-7-metil-5-(3-nitro-piridin-4-il)-

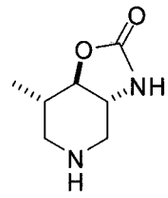
2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo (62 por ciento). LCMS (*m/z*): 379.0 (MH^+) a los 0.58 minutos.

Síntesis de (3aR,7R,7aS)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo



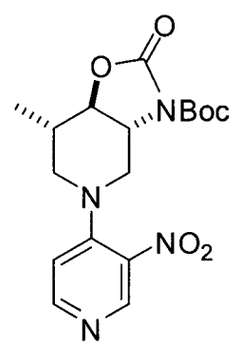
A una solución del (3aR,7R,7aS)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando el (3aR,7R,7aS)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.06 minutos.

Síntesis de (3aR,7S,7aR)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona



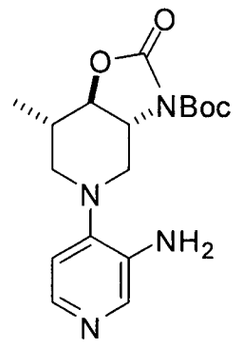
A una solución de la (3aR,7S,7aR)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó hidróxido de paladio al 20 por ciento sobre carbón (0.3 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 2 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la (3aR,7S,7aR)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (99 por ciento). LCMS (*m/z*): 157.1 (MH^+) a los 0.17 minutos.

Síntesis de (3aR,7S,7aR)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo



Una solución de 4-cloro-3-nitro-piridina (1.3 equivalentes) y (3aR,7S,7aR)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (1.5 equivalentes) en CH_2Cl_2, en una concentración de 0.1 M, se agitó a temperatura ambiente durante 48 horas, a lo cual se le agregó piperidina (0.4 equivalentes), para consumir el exceso de 4-cloro-3-nitro-piridina. Después de agitar durante 2 horas adicionales, se agregaron dicarbonato de diterbutilo (2.0 equivalentes) y dimetil-amino-piridina (0.1 equivalentes). Después de agitar durante 4 horas, la solución se dividió entre EtOAc y $NaHCO_3$ saturado, se lavó adicionalmente con $NaHCO_3$ saturado y NaCl saturado, se secó sobre $MgSO_4$, se filtró, y se purificó mediante cromatografía en gel de sílice (eluyente del 75 por ciento de EtOAc/hexanos), proporcionando el (3aR,7S,7aR)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo (35 por ciento). LCMS (*m/z*): 379.0 (MH^+). LC R_t = 2.42 minutos.

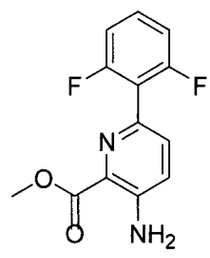
<u>Síntesis de (3aR,7R,7aS)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo</u>



A una solución del (3aR,7S,7aR)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 14 horas. En este tiempo, la mezcla se filtró a través de una almohadilla de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando el (3aR,7S,7aR)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de ter-butilo. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.18 minutos.

Método 1

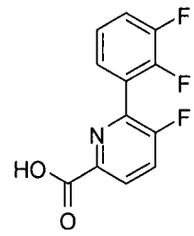
Síntesis de 3-amino-6-(2,6-difluoro-fenil)-picolinato de metilo



Una solución del 3-amino-6-bromo-picolinato de metilo (1.0 equivalentes), ácido 2,6-difluoro-fenil-borónico (3.0 equivalentes), y Pd(dppf)Cl_2-DCM (0.1 equivalentes) en 3:1 de DME / Na_2CO_3 2M (0.5 M) se sometió a irradiación con microondas a 120°C por intervalos de 15 minutos. La reacción se filtró y se lavó con EtOAc. La capa orgánica se dividió con

H_2O (25 mililitros), se lavó adicionalmente con NaCl (saturado) (25 mililitros), se secó sobre $MgSO_4$, y los volátiles se removieron al vacío. El residuo se diluyó en EtOAc, y se pasó a través de un tapón de gel de sílice, y los volátiles se removieron al vacío, proporcionando el 3-amino-6-(2,6-difluoro-fenil)-picolinato de metilo (47 por ciento). LCMS (*m/z*): 265.1 (MH^+); LC R_t = 2.70 minutos.

Síntesis de ácido 6-(2,3-difluoro-fenil)-5-fluoro-picolínico

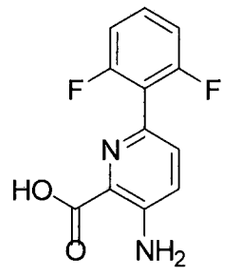


A una solución del ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes) en DME y Na_2CO_3 2M (3:1, 0.25 M), se le agregaron ácido 2,3-difluoro-fenil-borónico (1.3 equivalentes), y Pd(dppf)Cl_2-DCM (0.05 equivalentes) en un frasco para microondas. El frasco se calentó en el reactor de microondas a 120°C durante 30 minutos. La mezcla se diluyó con acetato de etilo, y se le agregó NaOH 1N. La fase orgánica se separó y se extrajo tres veces más con NaOH 1N y una vez con NaOH 6N. Las fases acuosas combinadas se filtraron y se acidificaron a un pH de 1 mediante la adición de HCl concentrado, y se extrajeron con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró, para dar el ácido

6-(2,3-difluoro-fenil)-5-fluoro-picolínico en un 78 por ciento. LC/MS = 254.1 (M+H), Rt = 0.75 minutos.

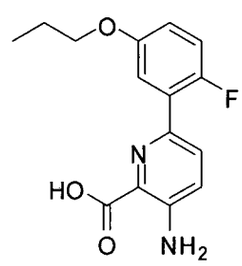
Método 2

Síntesis de ácido 3-amino-6-(2,6-difluoro-fenil)-picolínico



A una solución del 3-amino-6-(2,6-difluoro-fenil)-picolinato de metilo (1.0 equivalentes) en tetrahidrofurano (0.5 M), se le agregó LiOH 1M (4.0 equivalentes). Después de agitar durante 4 horas a 60°C, se agregó HCl 1N (4.0 equivalentes), y el tetrahidrofurano se removió al vacío. El sólido resultante se filtró y se enjuagó con H_2O fría (20 mililitros, 3 veces), para proporcionar el ácido 3-amino-6-(2,6-difluoro-fenil)-picolínico (90 por ciento). LCMS (*m/z*): 251.1 (MH^+); LC R_t = 2.1 minutos.

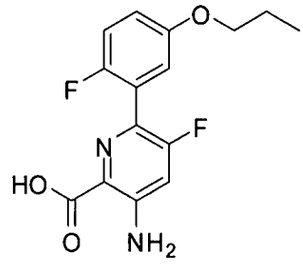
Síntesis de ácido 3-amino-6-(2-fluoro-5-propoxi-fenil)-picolínico



Se siguió el Método 1 utilizando el ácido 3-amino-6-

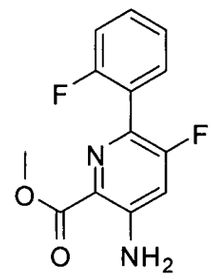
bromo-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-propoxi-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 3-amino-6-(2-fluoro-5-propoxi-fenil)-picolínico en un 75 por ciento de rendimiento. LC/MS = 291.0 (M+H), Rt = 0.81 minutos.

Síntesis de ácido 3-amino-5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolínico



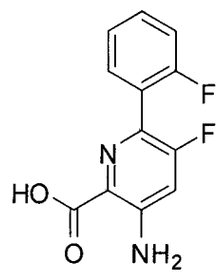
Se siguió el Método 1 utilizando el ácido 3-amino-6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-propoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 3-amino-5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolínico en un 28 por ciento de rendimiento. LC/MS = 309.1 (M+H), Rt = 1.00 minutos.

Síntesis de 3-amino-5-fluoro-6-(2-fluoro-fenil)-picolinato de metilo



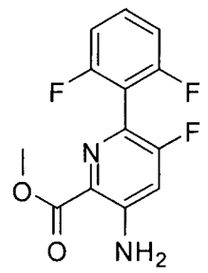
Se siguió el Método 1 utilizando el 3-amino-6-bromo-5-fluoro-picolinato de metilo (1.0 equivalentes), y el ácido 2-fluoro-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el 3-amino-5-fluoro-6-(2-fluoro-fenil)-picolinato de metilo en >99 por ciento de rendimiento. LC/MS = 265.0 (M+H), Rt = 0.77 minutos.

Síntesis de ácido 3-amino-5-fluoro-6-(2-fluoro-fenil)-picolínico



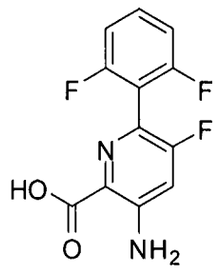
Se siguió el Método 2 utilizando el 3-amino-5-fluoro-6-(2-fluoro-fenil)-picolinato de metilo (1.0 equivalentes), y LiOH (5.0 equivalentes), para dar el ácido 3-amino-5-fluoro-6-(2-fluoro-fenil)-picolínico en un 90 por ciento de rendimiento. LC/MS = 251.1 (M+H), Rt = 0.80 minutos.

Síntesis de 3-amino-6-(2,6-difluoro-fenil)-5-fluoro-picolinato de metilo



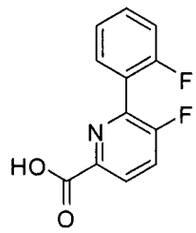
Se siguió el Método 1 utilizando el 3-amino-6-bromo-5-fluoro-picolinato de metilo (1.0 equivalentes), y el ácido 2,6-difluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el 3-amino-6-(2,6-difluoro-fenil)-5-fluoro-picolinato de metilo en un 94 por ciento de rendimiento. LC/MS = 283.0 (M+H), Rt = 0.76 minutos.

Síntesis de ácido 3-amino-6-(2,6-difluoro-fenil)-5-fluoro-picolínico



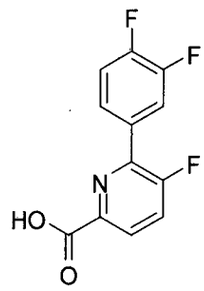
Se siguió el Método 2 utilizando el 3-amino-6-(2,6-difluoro-fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes), y LiOH (1.0 equivalentes), para dar el ácido 3-amino-6-(2,6-difluoro-fenil)-5-fluoro-picolínico en un 79 por ciento de rendimiento. LC/MS = 269.0 (M+H), Rt = 0.79 minutos.

Síntesis de ácido 5-fluoro-6-(2-fluoro-fenil)-picolínico



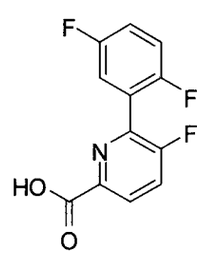
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 5-fluoro-6-(2-fluoro-fenil)-picolínico en un 43 por ciento de rendimiento. LC/MS = 236.1 (M+H), Rt = 0.72 minutos.

Síntesis de ácido 6-(3,4-difluoro-fenil)-5-fluoro-picolínico



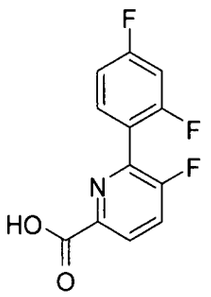
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 3,4-difluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 6-(3,4-difluoro-fenil)-5-fluoro-picolínico en un 70 por ciento de rendimiento. LC/MS = 254.1 (M+H), Rt = 0.81 minutos.

Síntesis de ácido 6-(2,5-difluoro-fenil)-5-fluoro-picolínico



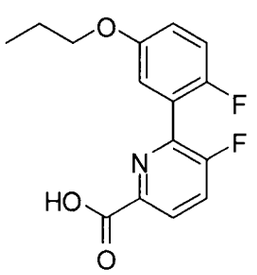
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y ácido 2,5-difluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 6-(2,5-difluoro-fenil)-5-fluoro-picolínico en un 80 por ciento de rendimiento. LC/MS = 254.1 (M+H), Rt = 0.74 minutos.

Síntesis de ácido 6-(2,4-difluoro-fenil)-5-fluoro-picolínico



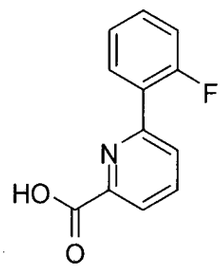
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 2,4-difluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 6-(2,4-difluoro-fenil)-5-fluoro-picolínico en un 79 por ciento de rendimiento. LC/MS = 254.1 (M+H), Rt = 0.75 minutos.

Síntesis de ácido 5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolínico



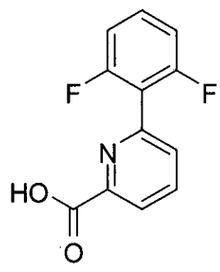
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-propoxi-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolínico. LC/MS = 294.2 (M+H), Rt = 0.95 minutos.

Síntesis de ácido 6-(2-fluoro-fenil)-picolínico



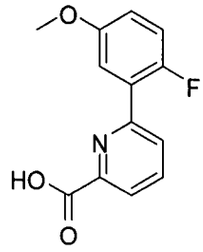
Se siguió el Método 1 utilizando el ácido 6-bromo-picolínico (1.0 equivalentes), y el ácido 2-fluoro-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 6-(2-fluoro-fenil)-picolínico en un 93 por ciento de rendimiento. LC/MS = 218.0 (M+H), Rt = 0.66 minutos.

Síntesis de ácido 6-(2,6-difluoro-fenil)-picolínico



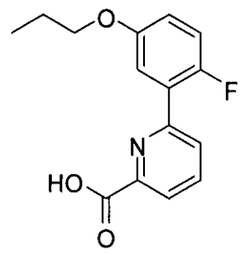
Se siguió el Método 1 utilizando el ácido 6-bromo-picolínico (1.0 equivalentes), y el ácido 2,6-difluoro-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 6-(2,6-difluoro-fenil)-picolínico en un 38 por ciento de rendimiento. LC/MS = 236.0 (M+H), Rt = 0.87 minutos.

Síntesis de ácido 6-(2-fluoro-5-metoxi-fenil)-picolínico



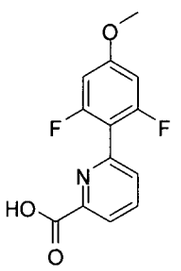
Se siguió el Método 1 utilizando el ácido 6-bromo-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-metoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-(2-fluoro-5-metoxi-fenil)-picolínico en un 95 por ciento de rendimiento. LC/MS = 248.2 (M+H), Rt = 0.78 minutos.

Síntesis de ácido 6-(2-fluoro-5-propoxi-fenil)-picolínico



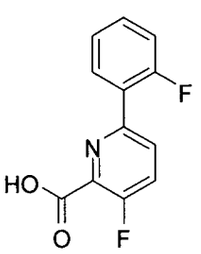
Se siguió el Método 1 utilizando el ácido 6-bromo-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-propoxi-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-(2-fluoro-5-propoxi-fenil)-picolínico en un 20 por ciento de rendimiento. LC/MS = 276.0 (M+H), Rt = 0.87 minutos.

Síntesis de ácido 6-(2,6-difluoro-4-metoxi-fenil)-picolínico



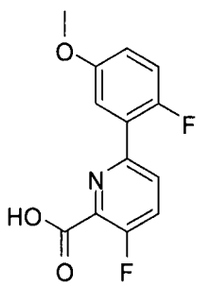
Se siguió el Método 1 utilizando el ácido 6-bromo-picolínico (1.0 equivalentes), y el ácido 2,6-difluoro-4-metoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-(2,6-difluoro-4-metoxi-fenil)-picolínico en un 42 por ciento de rendimiento. LC/MS = 266.1 (M+H), Rt = 0.75 minutos.

Síntesis de ácido 3-fluoro-6-(2-fluoro-fenil)-picolínico



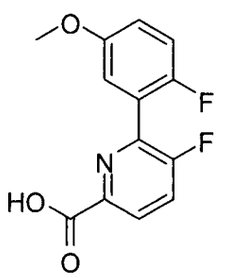
Se siguió el Método 1 utilizando el ácido 6-bromo-3-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-fenil-borónico (1.5 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), para dar el ácido 3-fluoro-6-(2-fluoro-fenil)-picolínico en un 81 por ciento de rendimiento. LC/MS = 236.1 (M+H), Rt = 0.72 minutos.

Síntesis de ácido 3-fluoro-6-(2-fluoro-5-metoxi-fenil)-picolínico



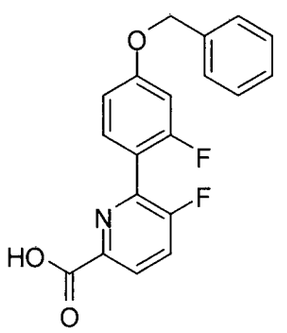
Se siguió el Método 1 utilizando el ácido 6-bromo-3-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-metoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 3-fluoro-6-(2-fluoro-5-metoxi-fenil)-picolínico en un rendimiento del 89 por ciento. LC/MS = 266.1 (M+H), Rt = 0.79 minutos.

Síntesis de ácido 5-fluoro-6-(2-fluoro-5-metoxi-fenil)-picolínico



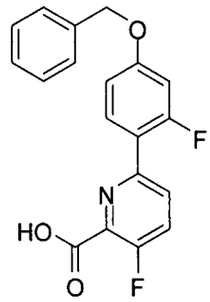
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 2-fluoro-5-metoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 5-fluoro-6-(2-fluoro-5-metoxi-fenil)-picolínico en un 86 por ciento de rendimiento. LC/MS = 266.1 (M+H), Rt = 0.79 minutos.

Síntesis de ácido 6-(4-(benciloxi)-2-fluoro-fenil)-5-fluoro-picolínico



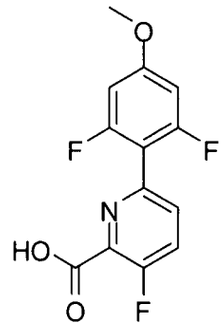
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el ácido 4-(benciloxi)-2-fluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-(4-(benciloxi)-2-fluoro-fenil)-5-fluoro-picolínico en un 28 por ciento de rendimiento. LC/MS = 342.1 (M+H), Rt = 1.05 minutos.

Síntesis de ácido 6-(4-(benciloxi)-2-fluoro-fenil)-3-fluoro-picolínico



Se siguió el Método 1 utilizando el ácido 6-bromo-3-fluoro-picolínico (1.0 equivalentes), y el ácido 4-(benciloxi)-2-fluoro-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-(4-(benciloxi)-2-fluoro-fenil)-3-fluoro-picolínico en un 41 por ciento de rendimiento. LC/MS = 342.1 (M+H), Rt = 1.06 minutos.

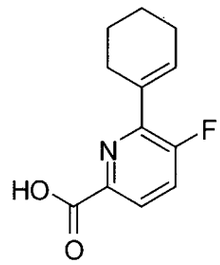
Síntesis de ácido 6-(2,6-difluoro-4-metoxi-fenil)-3-fluoro-picolínico



Se siguió el Método 1 utilizando el ácido 6-bromo-3-fluoro-picolínico (1.0 equivalentes), y el ácido 2,6-difluoro-4-metoxi-fenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM

(0.15 equivalentes), para dar el ácido 6-(2,6-difluoro-4-metoxi-fenil)-3-fluoro-picolínico en un 9 por ciento de rendimiento. LC/MS = 284.0 (M+H), Rt = 0.74 minutos.

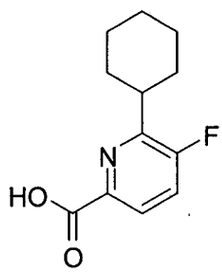
Síntesis de ácido 6-ciclohexenil-5-fluoro-picolínico



Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y ácido ciclohexenil-borónico (1.3 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.15 equivalentes), para dar el ácido 6-ciclohexenil-5-fluoro-picolínico en un 61 por ciento de rendimiento. LC/MS = 222.0 (M+H), Rt = 0.52 minutos.

Método 3

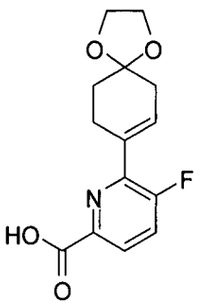
Síntesis de ácido 6-ciclohexil-5-fluoro-picolínico



A una solución desgasificada del ácido 6-ciclohexenil-5-

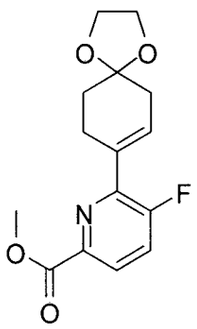
fluoro-picolínico (1.0 equivalentes) en metanol (0.07M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes), y la reacción se agitó bajo un globo de hidrógeno durante la noche. La solución entonces se filtró, se enjuagó con MeOH, y el filtrado se concentró para proporcionar el ácido 6-ciclohexil-5-fluoro-picolínico en un 65 por ciento de rendimiento. LC/MS = 224.2 (M+H), Rt = 0.95 minutos.

Síntesis de ácido 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolínico



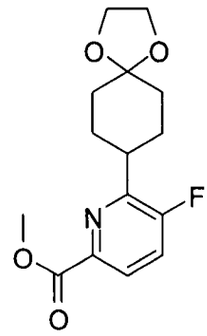
Se siguió el Método 1 utilizando el ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes), y el 4,4,5,5-tetrametil-2-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-1,3,2-dioxaborolano (2.0 equivalentes), y $Pd(dppf)Cl_2$-DCM (0.2 equivalentes), para dar el ácido 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolínico. LC/MS = 280.2 (M+H), Rt = 0.66 minutos.

Síntesis de 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolinato de metilo



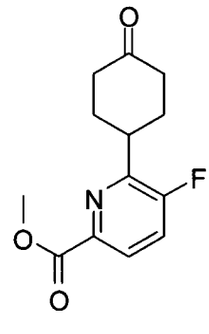
A una solución del ácido 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolínico (1.0 equivalentes) en dicloro-metano (0.3 M), se le agregaron EDC-HCl (1.0 equivalentes), DMAP (1.0 equivalentes), y metanol (10 equivalentes). La mezcla de reacción se dejó agitándose a temperatura ambiente durante 5 días, entonces se diluyó con acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con del 25 al 50 por ciento de acetato de etilo en hexanos, para proporcionar el 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolinato de metilo como el producto deseado en un 35 por ciento de rendimiento. LC/MS = 294.2 (M+H), Rt = 0.79 minutos.

Síntesis de 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-decan-8-il)-picolinato de metilo



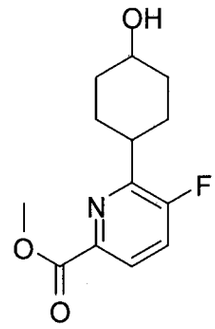
A una solución desgasificada del 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-dec-7-en-8-il)-picolinato de metilo (1.0 equivalentes) en metanol (0.07M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes), y la reacción se agitó bajo un globo de hidrógeno durante la noche. La solución entonces se filtró, se enjuagó con MeOH, y el filtrado se concentró, para proporcionar el 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-decan-8-il)-picolinato de metilo en un 91 por ciento de rendimiento. LC/MS = 296.2 (M+H), Rt = 0.83 minutos.

Síntesis de 5-fluoro-6-(4-oxo-ciclohexil)-picolinato de metilo



A una solución del 5-fluoro-6-(1,4-dioxa-espiro-[4.5]-decan-8-il)-picolinato de metilo (1.0 equivalentes) en acetona y agua (1:1, 0.04 M), se le agregó deshidrato de ácido oxálico (2.0 equivalentes), y la mezcla de reacción se agitó durante 3 días. La solución entonces se neutralizó mediante la adición de $NaHCO_3$ sólido, la mezcla se le agregó a acetato de etilo y salmuera, la fase orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró. Se obtuvo el 5-fluoro-6-(4-oxo-ciclohexil)-picolinato de metilo en un 98 por ciento de rendimiento. LC/MS = 252.1 (M+H), Rt = 0.68 minutos.

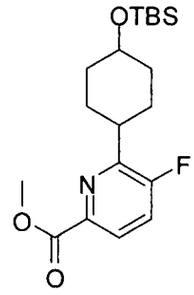
Síntesis de 5-fluoro-6-(4-hidroxi-ciclohexil)-picolinato de metilo



A una solución a 0°C de 5-fluoro-6-(4-oxo-ciclohexil)-picolinato de metilo (1.0 equivalentes) con metanol (0.08 M), se le agregó $NaBH_4$. La solución se dejó calentar a temperatura ambiente durante la noche, entonces se dividió entre acetato de etilo y salmuera, la fase orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró, para dar el 5-fluoro-6-(4-hidroxi-ciclohexil)-picolinato de metilo como una mezcla de dos

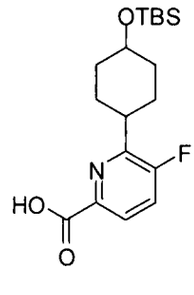
isómeros (5:1). LC/MS = 254.2 (M+H), Rt = 0.63 minutos.

Síntesis de 6-(4-(ter-butil-dimetil-sililoxi)-ciclohexil)-5-fluoro-picolinato de metilo



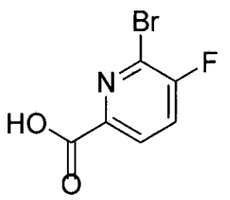
A una solución del 5-fluoro-6-(4-hidroxi-ciclohexil)-picolinato de metilo (1.0 equivalentes) en N,N-dimetil-formamida (0.15 M), se le agregaron imidazol (4.0 equivalentes), y TBDMSCl (2.5 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 2 días, entonces se agregó a acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró, para dar el 6-(4-(ter-butil-dimetil-sililoxi)-ciclohexil)-5-fluoro-picolinato de metilo en un 97 por ciento de rendimiento como una mezcla de isómeros (3:1). LC/MS = 368.3 (M+H), Rt = 1.4 y 1.42 minutos.

Síntesis de ácido 6-(4-(ter-butil-dimetil-sililoxi)-ciclohexil)-5-fluoro-picolínico



A una solución del 6-(4-(ter-butil-dimetil-sililoxi)-ciclohexil)-5-fluoro-picolinato de metilo (1.0 equivalentes) en THF/MeOH (2:1, 0.09 M), se le agregó LiOH (1.5 equivalentes). La mezcla de reacción se agitó durante la noche a temperatura ambiente, entonces se agregaron HCl 1N y acetato de etilo, la fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró, para dar el ácido 6-(4-(ter-butil-dimetil-sililoxi)-ciclohexil)-5-fluoro-picolínico como una mezcla de isómeros (3:1) en un 82 por ciento de rendimiento. LC/MS = 354.2 (M+H), Rt = 1.38 y 1.41 minutos.

Síntesis de ácido 6-bromo-5-fluoro-picolínico

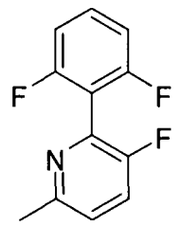


A la 2-bromo-3-fluoro-6-metil-piridina (1.0 equivalentes) en H_2O (30 mililitros), se le agregó permanganato de potasio (1.0 equivalentes). La solución se calentó a 100°C durante 5 horas, en cuyo tiempo, se agregó más permanganato de potasio (1.0 equivalentes). Después de calentar durante 48 horas adicionales, el material se filtró a través de Celite (4 centímetros x 5.08 centímetros), y se enjuagó con H_2O (150 mililitros). La fase acuosa combinada se acidificó con HCl 1N hasta un pH = 4, se extrajo con acetato de etilo (200 mililitros),

se lavó con NaCl (saturado), se secó sobre $MgSO_4$, se filtró, y se concentró, para proporcionar el ácido 6-bromo-5-fluoro-picolínico (17 por ciento) como un sólido blanco. LCMS (m/z): 221.9 (MH+); LC Rt = 2.05 minutos.

Método 4

Síntesis de 2-(2,6-difluoro-fenil)-3-fluoro-6-metil-piridina

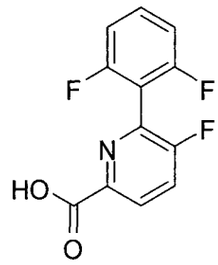


A una solución de la 2-bromo-3-fluoro-6-metil-piridina (1.0 equivalentes) en tetrahidrofurano y agua (10:1, 0.2 M), se le agregaron el ácido 2,6-difluoro-fenil-borónico (2.0 equivalentes), y fluoruro de potasio (3.3 equivalentes). La reacción se desgasificó durante 10 minutos, entonces se agregó $Pd_2(dba)_3$ (0.05 equivalentes), seguido por tri-ter-butil-fosfina (0.1 equivalentes). La reacción se agitó a 60°C durante 1 hora, en cuyo punto, se consumió todo el material de partida, como fue indicado por la LC/MS. La reacción se dejó enfriar a temperatura ambiente, se dividió con acetato de etilo y agua, la fase orgánica se secó con sulfato de sodio, se filtró, y se concentró. El material crudo se diluyó en EtOH hasta 0.1 M, y se agregaron 0.5 equivalentes de $NaBH_4$ para reducir el dba. La reacción se agitó durante una hora a temperatura ambiente,

entonces se apagó con agua, y se concentró al vacío, para remover el etanol. El producto se extrajo en éter, se lavó con salmuera, los orgánicos se secaron sobre sulfato de sodio, se filtraron, y se concentraron. El material crudo se cargó sobre gel de sílice, y se purificó mediante cromatografía en columna (ISCO) eluyendo con hexanos y acetato de etilo (del 0 por ciento al 10 por ciento de acetato de etilo). Las fracciones puras se combinaron y se concentraron, para proporcionar la 2-(2,6-difluoro-fenil)-3-fluoro-6-metil-piridina como un aceite amarillo claro en un 86 por ciento de rendimiento. LC/MS = 224.0 (M+H), Rt = 0.84 minutos.

Método 5

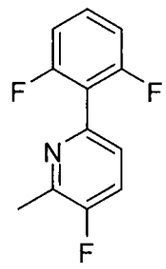
Síntesis de ácido 6-(2,6-difluoro-fenil)-5-fluoro-picolínico



A una solución de la 2-(2,6-difluoro-fenil)-3-fluoro-6-metil-piridina (1.0 equivalentes) en agua (0.05 M), se le agregó $KMnO_4$ (2.0 equivalentes), y la reacción se calentó a reflujo durante la noche. Se agregaron otros 2.0 equivalentes de $KMnO_4$, y se agitó a reflujo durante otras 8 horas. La solución se enfrió a temperatura ambiente, se filtró a través de Celite, y

se lavó con agua. El filtrado se acidificó con HCl 6 N a un pH = 3, el precipitado blanco se filtró. El filtrado se acidificó adicionalmente a un pH = 1, y se filtró nuevamente. El filtrado se extrajo con acetato de etilo hasta que ya no hubo más producto en la capa acuosa. La fase orgánica se lavó con salmuera y se secó sobre sulfato de magnesio, se filtró, y se concentró. El residuo se disolvió en acetato de etilo, se lavó con NaOH 1N, la capa acuosa se acidificó a un pH = 1, y los cristales blancos se filtraron. Los productos combinados proporcionaron el ácido 6-(2,6-difluoro-fenil)-5-fluoro-picolínico en un 32 por ciento de rendimiento como un sólido blanco. LC/MS = 254.0 (M+H), Rt = 0.71 minutos.

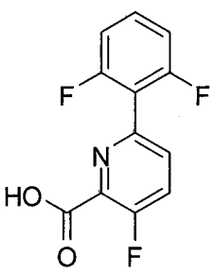
Síntesis de 6-(2,6-difluoro-fenil)-3-fluoro-2-metil-piridina



A una solución de la 6-bromo-3-fluoro-2-metil-piridina (1.0 equivalentes) en etanol y tolueno (1:1, 0.2 M), se le agregaron ácido 2,6-difluoro-fenil-borónico, DIEA (5 equivalentes), y $Pd(PPh_3)_4$ (0.2 equivalentes). La reacción se calentó en el reactor de microondas a 120°C durante 30 minutos. La solución se filtró y se enjuagó con acetato de etilo. Los volátiles se

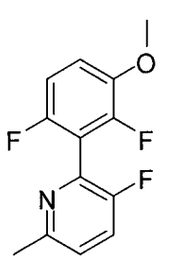
removieron al vacío, y el producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (del 2.5 al 20 por ciento de acetato de etilo). Después de la concentración de las fracciones puras, se aisló la 6-(2,6-difluoro-fenil)-3-fluoro-2-metil-piridina en un 88 por ciento de rendimiento. LC/MS = 224.1 (M+H), Rt = 0.87 minutos.

Síntesis de ácido 6-(2,6-difluoro-fenil)-3-fluoro-picolínico



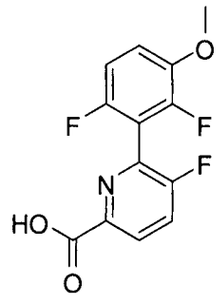
Se siguió el Método 5 utilizando la 6-(2,6-difluoro-fenil)-3-fluoro-2-metil-piridina (1.0 equivalentes), y permanganato de potasio (6.0 equivalentes), para dar el ácido 6-(2,6-difluoro-fenil)-3-fluoro-picolínico en un 30 por ciento de rendimiento. LC/MS = 254.1 (M+H), Rt = 0.70 minutos.

Síntesis de 2-(2,6-difluoro-3-metoxi-fenil)-3-fluoro-6-metil-piridina



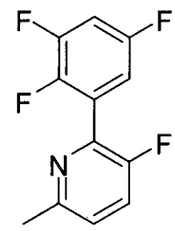
Se siguió el Método 4 utilizando la 2-bromo-3-fluoro-6-metil-piridina (1.0 equivalentes), y el ácido 2,6-difluoro-3-metoxi-fenil-borónico (2.0 equivalentes), para dar la 2-(2,6-difluoro-3-metoxi-fenil)-3-fluoro-6-metil-piridina en un 60 por ciento de rendimiento. LC/MS = 254.1 (M+H), Rt = 0.85 minutos.

Síntesis de ácido 6-(2,6-difluoro-3-metoxi-fenil)-5-fluoro-picolínico



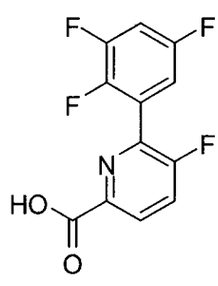
Se siguió el Método 5 utilizando la 2-(2,6-difluoro-3-metoxi-fenil)-3-fluoro-6-metil-piridina (1.0 equivalentes), y permanganato de potasio (4.0 equivalentes), para dar el ácido 6-(2,6-difluoro-3-metoxi-fenil)-5-fluoro-picolínico en un 27 por ciento de rendimiento. LC/MS = 284.1 (M+H), Rt = 0.75 minutos.

Síntesis de 3-fluoro-6-metil-2-(2,3,5-trifluoro-fenil)-piridina



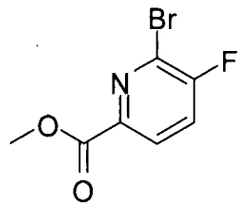
A una solución de la 2-bromo-3-fluoro-6-metil-piridina (1.0 equivalentes) en dioxano (0.2 M), se le agregaron el ácido 2,3,5-trifluoro-fenil-borónico, y $Pd(dppf)Cl_2$-DCM (0.1 equivalentes). Se agregó carbonato de sodio acuoso (solución 2M, 2.0 equivalentes), y la reacción se calentó en el reactor de microondas a 120°C durante 15 minutos. La solución se dividió entre acetato de etilo y $NaHCO_3$ saturado, la fase orgánica se lavó con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (1:3), para dar la 3-fluoro-6-metil-2-(2,3,5-trifluoro-fenil)-piridina en un 87 por ciento de rendimiento. LC/MS = 242.1 (M+H), Rt = 0.98 minutos.

Síntesis de ácido 5-fluoro-6-(2,3,5-trifluoro-fenil)-picolínico



A una solución de la 3-fluoro-6-metil-2-(2,3,5-trifluoro-fenil)-piridina (1.0 equivalentes) en agua y t-BuOH (2:1, 0.06 M), se le agregó permanganato de potasio (10 equivalentes), y la solución se calentó a 90°C durante 5 horas. Después de enfriarse a temperatura ambiente, la solución se filtró, y el filtrado se concentró bajo presión reducida, para proporcionar el ácido 5-fluoro-6-(2,3,5-trifluoro-fenil)-picolínico en un rendimiento del 89 por ciento. LC/MS = 272.0 (M+H), Rt = 0.80 minutos.

Síntesis de 6-bromo-5-fluoro-picolinato de metilo

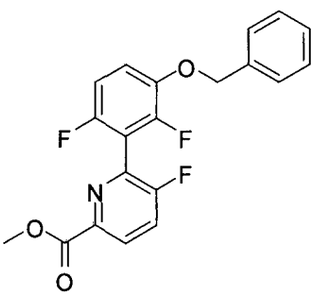


A una solución del ácido 6-bromo-5-fluoro-picolínico (1.0 equivalentes) en metanol (0.2 M), se le agregó H_2SO_4 (4.2 equivalentes), y la reacción se agitó a temperatura ambiente durante dos horas. Al completarse la reacción, como se monitoreó mediante LC/MS, la reacción se diluyó con acetato de etilo, y se apagó lentamente con $NaHCO_3$ acuoso saturado. La reacción se vertió en un embudo de separación, y se extrajo con acetato de etilo. La fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró al vacío, para proporcionar el 6-bromo-5-fluoro-picolinato de metilo como un sólido blanco

(>99 por ciento). LC/MS = 233.9/235.9 (M+H), Rt = 0.69 minutos.

Método 6

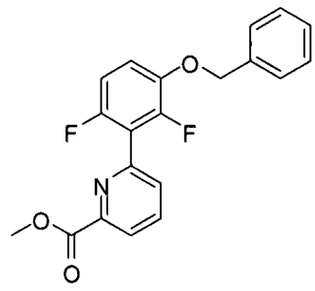
Síntesis de 6-(3-(benciloxi)-2,6-difluoro-fenil)-5-fluoro-picolinato de metilo



A una solución del 6-bromo-5-fluoro-picolinato de metilo (1.0 equivalentes) en tetrahidrofurano y agua (10:1, 0.1 M), se le agregó el ácido 3-(benciloxi)-2,6-difluoro-fenil-borónico (2.5 equivalentes), y fluoruro de potasio (3.3 equivalentes). La reacción se desgasificó con nitrógeno, entonces se agregaron $Pd_2(dba)_3$ (0.25 equivalentes), y tri-ter-butil-fosfina (0.5 equivalentes), y la reacción se calentó a 80°C durante una hora. El análisis de LC/MS indicó la conversión completa del material de partida hasta el producto. La reacción se enfrió a temperatura ambiente, entonces se concentró al vacío, y se fusionó con gel de sílice. El producto crudo se purificó mediante cromatografía por evaporación instantánea ISCO, eluyendo con acetato de etilo y hexanos (del 0 por ciento al 30 por ciento de acetato de etilo), para proporcionar el 6-(3-

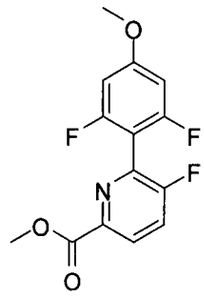
(benciloxi)-2,6-difluoro-fenil)-5-fluoro-picolinato de metilo como el producto deseado como un aceite amarillo claro en un 96 por ciento de rendimiento. LC/MS = 374.0 (M+H), Rt = 1.07 minutos.

Síntesis de 6-(3-(benciloxi)-2,6-difluoro-fenil)-picolinato de metilo



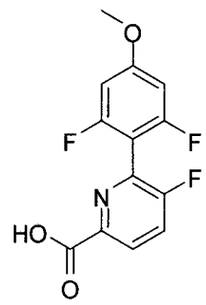
Se siguió el Método 6 utilizando el 6-bromo-picolinato de metilo (1.0 equivalentes), y el ácido 3-(benciloxi)-2,6-difluoro-fenil-borónico (2.5 equivalentes), para dar el 6-(3-(benciloxi)-2,6-difluoro-fenil)-picolinato de metilo como un sólido amarillo claro en un 95 por ciento de rendimiento. LC/MS = 356.2 (M+H), Rt = 1.03 minutos.

Síntesis de 6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolinato de metilo



Se siguió el Método 6 utilizando el 6-bromo-picolinato de metilo (1.0 equivalentes), y el ácido 2,6-difluoro-4-metoxi-fenil-borónico (2.5 equivalentes), para dar el 6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolinato de metilo como un sólido blanco en un 85 por ciento de rendimiento. LC/MS = 298.0 (M+H), Rt = 0.89 minutos.

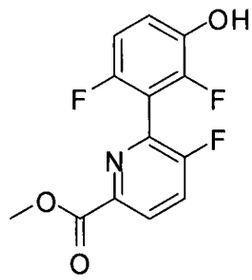
Síntesis de ácido 6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolínico



A una solución del 6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes) en THF/MeOH (2:1, 0.09 M), se le agregó LiOH (1.5 equivalentes), y la reacción se agitó a temperatura ambiente durante 1 hora. La solución se apagó con HCl 1N, se extrajo con acetato de etilo, se lavó con salmuera, se secó con sulfato de sodio, se filtró, y se concentró, para dar el ácido 6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolínico en un 84 por ciento de rendimiento. LC/MS = 284.1 (M+H), Rt = 0.76 minutos.

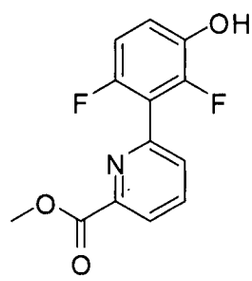
Método 7

Síntesis de 6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinato de metilo



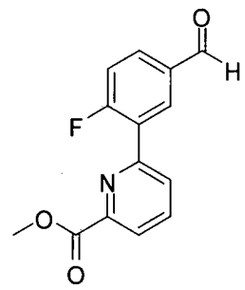
A una solución de 6-(3-(benciloxi)-2,6-difluoro-fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes) en metanol (0.1 M), se le agregó Pd/C al 10 por ciento (0.1 equivalentes) en acetato de etilo. La reacción se colocó bajo una atmósfera de hidrógeno, y se agitó durante 2 horas. Al completarse, la solución se filtró sobre una almohadilla de Celite, la almohadilla se lavó con metanol, y el filtrado se concentró al vacío, para dar el 6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinato de metilo como un aceite gris en un 86 por ciento de rendimiento. LC/MS = 284.0 (M+H), Rt = 0.90 minutos.

Síntesis de 6-(2,6-difluoro-3-hidroxi-fenil)-picolinato de metilo



Se siguió el Método 7 utilizando el 6-(3-(benciloxi)-2,6-difluoro-fenil)-picolinato de metilo (1.0 equivalentes), para proporcionar el 6-(2,6-difluoro-3-hidroxi-fenil)-picolinato de metilo como un sólido color café claro en un 96 por ciento de rendimiento. LC/MS = 266.0 (M+H), Rt = 0.68 minutos.

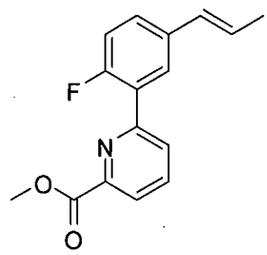
Síntesis de 6-(2-fluoro-5-formil-fenil)-picolinato de metilo



A una solución del 6-bromo-picolinato de metilo (1.0 equivalentes) en DME (0.03 M), en un frasco para microondas, se le agregaron $Pd(dppf)Cl_2$-DCM (0.05 equivalentes), ácido 2-fluoro-5-formil-fenil-borónico (1.5 equivalentes), y Na_2CO_3 2M (2 equivalentes). Los reactivos se calentaron hasta 120°C durante 20 minutos. Se detectó una mezcla del producto deseado y el ácido carboxílico correspondiente mediante LC/MS, la reacción se diluyó con acetato de etilo, se lavó con HCl (pH = 5), la fase ácida se extrajo con acetato de etilo, las capas orgánicas combinadas se secaron con sulfato de magnesio, se filtraron, y se concentraron al vacío, para proporcionar un sólido color café claro. El sólido se disolvió en metanol, y se trató con 3 equivalentes de TMS-diazometano a

temperatura ambiente. Después de la conversión completa del ácido carboxílico hasta el metil-éster correspondiente, la reacción se concentró al vacío, y el material crudo se purificó mediante cromatografía en columna de gel de sílice (ISCO) eluyendo con acetato de etilo al 30 por ciento en hexanos, para proporcionar el 6-(2-fluoro-5-formil-fenil)-picolinato de metilo como un sólido amarillo en un 58 por ciento de rendimiento. LC/MS = 260.0 (M+H), Rt = 0.70 minutos.

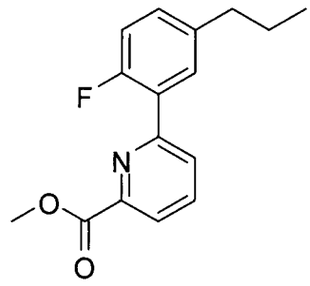
Síntesis de (E)-6-(2-fluoro-5-(prop-1-enil)-fenil)-picolinato de metilo



A una solución del 6-(2-fluoro-5-formil-fenil)-picolinato de metilo (1.0 equivalentes) en metanol (0.17 M), se le agregó bromuro de etil-trifenil-fosfonio (1.0 equivalentes), seguido por metóxido de sodio (1.5 equivalentes). La reacción se calentó a 65°C durante 5 horas, entonces se enfrió a temperatura ambiente, y se concentró al vacío. El material crudo se purificó mediante cromatografía en columna de gel de sílice (ISCO), eluyendo con acetato de etilo al 50 por ciento en hexanos, para proporcionar el (E)-6-(2-fluoro-5-(prop-1-enil)-fenil)-picolinato de metilo como un sólido blanco en un 81 por ciento de

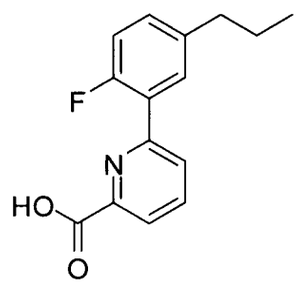
rendimiento. LC/MS = 272.0 (M+H), Rt = 0.73 minutos.

Síntesis de 6-(2-fluoro-5-propil-fenil)-picolinato de metilo



A una solución del (E)-6-(2-fluoro-5-(prop-1-enil)-fenil)-picolinato de metilo (1.0 equivalentes) en metanol (0.04 M) se le agregó Pd/C al 10 por ciento (0.5 equivalentes), y la reacción se colocó bajo una atmósfera de hidrógeno y se dejó agitándose durante la noche. La mezcla se filtró sobre una almohadilla de Celite, y se lavó con metanol. El filtrado se concentró al vacío, para proporcionar el 6-(2-fluoro-5-propil-fenil)-picolinato de metilo como un aceite color gris claro en un 97 por ciento de rendimiento. LC/MS = 274.2 (M+H), Rt = 0.61 minutos.

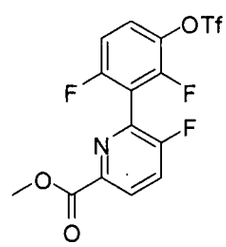
Síntesis de ácido 6-(2-fluoro-5-propil-fenil)-picolínico



A una solución del 6-(2-fluoro-5-propil-fenil)-picolinato de metilo (1.0 equivalentes) en tetrahidrofurano, se le agregó hidróxido de litio (10 equivalentes), y la reacción se agitó a temperatura ambiente durante 1 hora. El solvente de tetrahidrofurano se removió al vacío, y la fase básica restante se acidificó con HCl concentrado. La capa acuosa se extrajo con acetato de etilo (2 veces), la fase orgánica se secó con sulfato de sodio, se filtró, y se concentró, para dar el ácido 6-(2-fluoro-5-propil-fenil)-picolínico en un 35 por ciento de rendimiento. LC/MS = 260.2 (M+H), Rt = 0.36 minutos.

Método 8

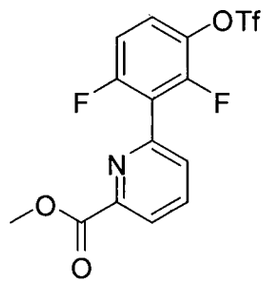
Síntesis de 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-5-fluoro-picolinato de metilo



A una solución del 6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes) en dicloro-metano (0.2 M), se le agregaron DIEA (2.0 equivalentes), y 1,1,1-trifluoro-N-fenil-N-(trifluoro-metil-sulfonil)-metan-sulfonamida (1.5 equivalentes). La reacción se dejó agitándose durante la noche a temperatura ambiente. La solución se apagó con agua, la

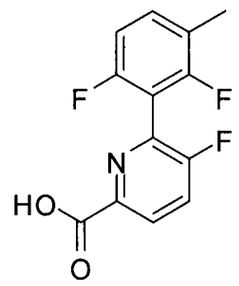
fase orgánica se secó con sulfato de sodio, y se concentró. El material crudo se purificó por medio de cromatografía ISCO, eluyendo con acetato de etilo y hexanos (del 0 al 30 por ciento de acetato de etilo). Las fracciones puras se concentraron para dar el 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-5-fluoro-picolinato de metilo como el producto deseado como un aceite transparente en un 68 por ciento de rendimiento. LC/MS = 416.1 (M+H), Rt = 1.08 minutos.

Síntesis de 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-picolinato de metilo



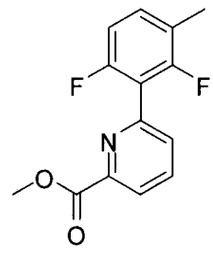
Se siguió el Método 8 utilizando el 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes), para proporcionar el 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-picolinato de metilo como un aceite incoloro, en >99 por ciento de rendimiento. LC/MS = 397.9 (M+H), Rt = 1.03 minutos.

Síntesis de ácido 6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolínico



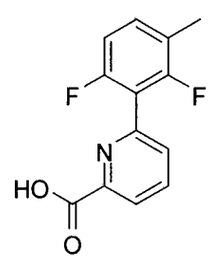
A una solución del 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi) fenil)-5-fluoro-picolinato de metilo (1.0 equivalentes) en dioxano y agua (10:1, 0.15 M), se le agregó ácido metil-borónico (3.0 equivalentes), y carbonato de potasio (3.0 equivalentes). La reacción se desgasificó con nitrógeno durante 10 minutos; entonces se agregó $Pd(PPh_3)_4$ (0.1 equivalentes) a la solución, y se calentó a 100°C durante 3 horas. La LC/MS de la reacción en este punto indicó la conversión completa hasta el producto de ácido carboxílico (M+H = 268). Se enfrió a temperatura ambiente, y se le agregaron agua y acetato de etilo. Las dos capas se separaron, la fase acuosa se acidificó con HCl concentrado a un pH = 1, y se extrajo con acetato de etilo. La fase orgánica se secó con sulfato de sodio, se filtró, y se concentró al vacío, para dar el ácido 6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolínico como un aceite transparente en un 97 por ciento de rendimiento. LC/MS = 268.1 (M+H), Rt = 0.82 minutos.

Síntesis de 6-(2,6-difluoro-3-metil-fenil)-picolinato de metilo



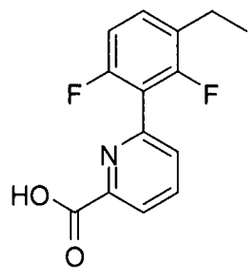
A una solución del 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-picolinato de metilo (1.0 equivalentes) en tolueno, se le agregó $Pd(dppf)Cl_2$-DCM (0.1 equivalentes), seguido por dimetil-zinc (3.0 equivalentes). La solución se convirtió desde un color naranja hasta un color amarillo brillante. La reacción se calentó a 80°C durante 2 horas, en cuyo tiempo, el análisis de LC/MS indicó la conversión completa hasta el producto. La reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo, y se lavó con salmuera. La capa orgánica se secó con sulfato de magnesio, se filtró, y se concentró al vacío, para proporcionar el 6-(2,6-difluoro-3-metil-fenil)-picolinato de metilo como un aceite color café en un rendimiento cuantitativo. LC/MS = 264.0 (M+H), Rt = 0.90 minutos.

Síntesis de ácido 6-(2,6-difluoro-3-metil-fenil)-picolínico



A una solución del 6-(2,6-difluoro-3-metil-fenil)-picolinato de metilo (1.0 equivalentes) en tetrahidrofurano, se le agregó hidróxido de sodio (10 equivalentes), y la reacción se agitó durante 2 horas. La solución se diluyó con acetato de etilo, y se lavó con NaOH 1N (2 veces). Los lavados acuosos básicos combinados se combinaron y se acidificaron con HCl concentrado. La fase acuosa ácida se extrajo con acetato de etilo (2 veces), las capas orgánicas combinadas se secaron con sulfato de magnesio, se filtraron, y se concentraron al vacío, para proporcionar el ácido 6-(2,6-difluoro-3-metil-fenil)-picolínico como un sólido blanco en un 85 por ciento de rendimiento. LC/MS = 250.0 (M+H), Rt = 0.76 minutos.

Síntesis de ácido 6-(3-etil-2,6-difluoro-fenil)-picolínico



A una solución del 6-(2,6-difluoro-3-(trifluoro-metil-sulfoniloxi)-fenil)-picolinato de metilo (1.0 equivalentes) en tolueno (0.15 M), se le agregó $Pd(dppf)Cl_2$-DCM (0.1 equivalentes), seguido por dietil-zinc (3.0 equivalentes). La solución se convirtió desde un color naranja hasta un color amarillo brillante. La reacción se calentó a 70°C durante 2

horas, en cuyo tiempo, el análisis de LC/MS indicó una mezcla de una proporción de 1:3:1 del producto hidrolizado, el producto deseado, y un subproducto desconocido. La reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo, y se lavó con NaOH 1N (2 veces). La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío, para proporcionar un aceite color café. El aceite se volvió a disolver en tetrahidrofurano, y se trató con NaOH 1N durante una hora. La reacción se diluyó entonces con acetato de etilo, y se lavó con NaOH 1N (2 veces). Los lavados básicos se combinaron, se acidificaron con HCl concentrado, y se extrajeron con acetato de etilo (3 veces). La fase orgánica se secó con sulfato de magnesio, se filtró, y se concentró al vacío, para proporcionar el ácido 6-(3-etil-2,6-difluoro-fenil)-picolínico como un aceite color café claro en >99 por ciento de rendimiento. LC/MS = 264.1 (M+H), Rt = 0.88 minutos.

Método 9

Una solución homogénea de 1 equivalente de cada uno de amina, ácido carboxílico, HOAT, y EDC en N,N-dimetil-formamida, en una concentración de 0.5 M, se dejó reposar durante 24 horas, en cuyo tiempo, se agregaron agua y acetato de etilo. La fase orgánica se secó con sulfato de sodio, y se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos para dar el producto

de amida protegida deseado. De una manera alternativa, la mezcla de reacción cruda se purificó directamente mediante HPLC. Después de la liofilización, se obtuvo la sal del ácido trifluoro-acético del producto de amida protegida. De una manera alternativa, las fracciones de la HPLC se pudieron agregar a EtOAc y Na_2CO_3 sólido, se separaron, y se lavaron con NaCl (saturado). Después de secarse sobre $MgSO_4$, de filtrarse, y de remover los volátiles al vacío, se obtuvo el producto de amida protegida como una base libre. De una manera alternativa, la mezcla de reacción cruda se utilizó para el paso de desprotección sin mayor purificación.

Si estuvo presente una amina protegida por N-Boc, se removió mediante el tratamiento con un exceso de HCl 4M / dioxano durante 14 horas, o mediante el tratamiento con ácido trifluoro-acético/CH_2Cl_2 al 25 por ciento durante 2 horas. Después de la remoción de los volátiles al vacío, el material se purificó mediante HPLC en fase inversa, proporcionando, después de la liofilización, el producto de amida como la sal de ácido trifluoro-acético. De una manera alternativa, las fracciones de la HPLC se pudieron agregar a EtOAc y Na_2CO_3 sólido, se separaron, y se lavaron con NaCl (saturado). Después de secarse sobre $MgSO_4$, de filtrarse, y de remover los volátiles al vacío, se obtuvo la base libre. Después de disolverse en MeCN/H_2O, de agregar 1 equivalente de HCl 1N, y de liofilizar, se obtuvo la sal de HCl del producto de amida.

Si estuvo presente un carbamato de N-Boc1,2-amino-alcohol cíclico, antes de la desprotección de Boc, se pudo disociar el carbamato cíclico mediante el tratamiento con Cs_2CO_3 (0.5 equivalentes) en etanol en una concentración de 0.1 M durante tres horas. Después de la remoción de los volátiles al vacío, se desprotegió el grupo Boc-amino como se describe anteriormente.

Si estuvieron presentes un N-Boc, o un grupo OAc, antes de la desprotección de Boc, el grupo acetato se pudo disociar mediante el tratamiento con K_2CO_3 (2.0 equivalentes) en etanol en una concentración de 0.1 M durante 24 horas.

Si estuvo presente un grupo N-ftalimida, la amina se desprotegió mediante el tratamiento con hidrazina en metanol a 65°C durante tres horas. Después de enfriarse y de filtrar el precipitado blanco, el filtrado se concentró y se purificó mediante HPLC en fase inversa, para proporcionar el producto de amino-amida.

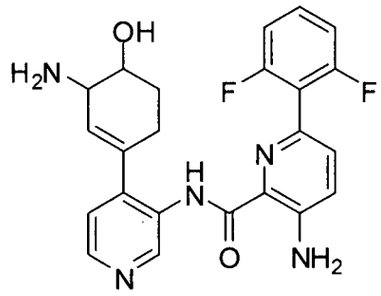
Si estuvo presente un éter TBDMS, se desprotegió antes de la remoción del Boc, mediante el tratamiento con HCl 6N, tetrahidrofurano, y metanol (1:2:1) a temperatura ambiente durante 12 horas. Después de la remoción de los volátiles al vacío, el grupo Boc-amino se desprotegió como se describe anteriormente. De una manera alternativa, el éter TBDMS y el grupo Boc se pudieron desproteger ambos con HCl 6N, tetrahidrofurano, y metanol (1:2:1) dejándose a temperatura

ambiente durante 24 horas, o calentándose a 60°C durante 3 horas.

Si estuvo presente un grupo OMe, se desprotegió mediante el tratamiento con BBr_3 1 M en dicloro-metano (2.0 equivalentes) durante 24 horas. Se agregó agua por goteo, y los volátiles se removieron al vacío. El material se purificó por medio de HPLC en fase inversa como se describe anteriormente.

Si estuvo presente un grupo OBn, se desprotegió mediante el tratamiento con Pd/C al 10 por ciento (0.2 equivalentes), bajo una atmósfera de hidrógeno en acetato de etilo y metanol (1:2). Al completarse, la reacción se filtró a través de Celite, se lavó con metanol, y el filtrado se concentró al vacío.

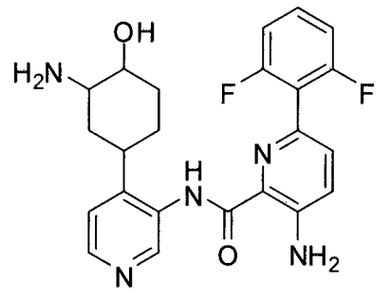
Síntesis de (+/-)-3-amino-N-(4-(3-amino-4-hidroxi-ciclohex-1-enil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida



Siguiendo el Método 9, el (+/-)-3-(3-amino-piridin-4-il)-6-(ter-butil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de ter-butilo y el ácido 3-amino-6-(2,6-difluoro-fenil)-picolínico se acoplaron

y se desprotegieron para proporcionar la (+/-)-3-amino-N-(4-(3-amino-4-hidroxi-ciclohex-1-enil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida como la sal de ácido trifluoro-acético. LCMS (*m/z*): 438.2 (MH^+), LC R_t = 2.00 minutos.

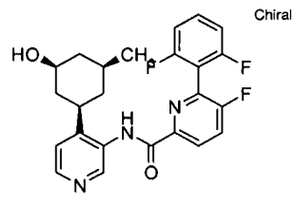
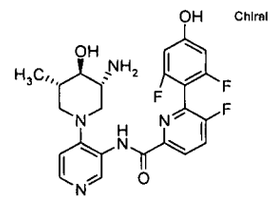
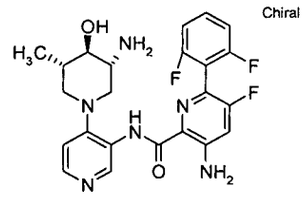
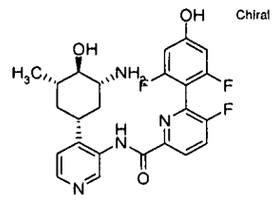
Síntesis de (+/-)-3-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida

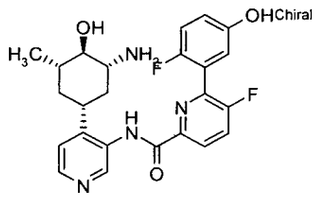
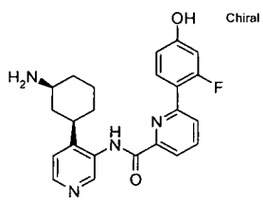
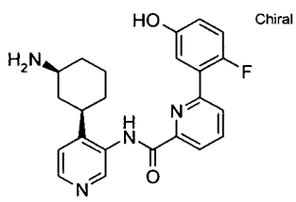
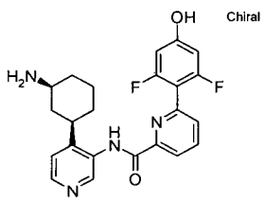


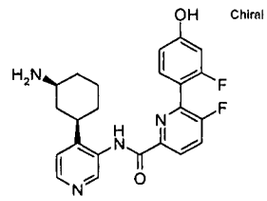
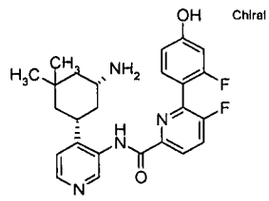
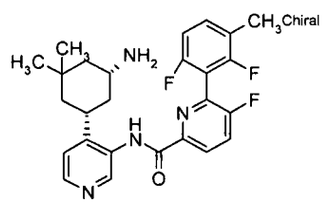
Siguiendo el Método 9, el (+/-)-5-(3-amino-piridin-4-il)-2-(ter-butil-dimetil-sililoxi)-ciclohexil-carbamato de ter-butilo y el ácido 3-amino-6-(2,6-difluoro-fenil)-picolínico se acoplaron y se desprotegieron para proporcionar la (+/-)-3-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida como la sal de ácido trifluoro-acético en un 18 por ciento de rendimiento. LCMS (*m/z*): 440.3 (MH^+), LC R_t = 2.04 minutos.

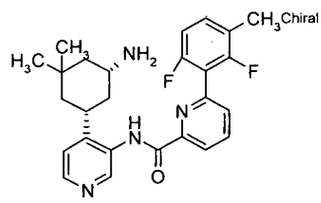
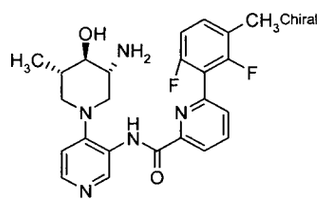
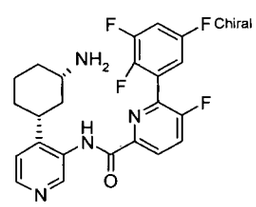
Siguiendo los procedimientos del Método 9, se prepararon los siguientes compuestos:

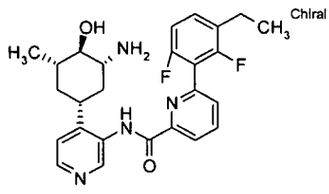
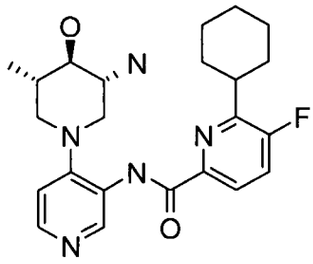
CUADRO 1

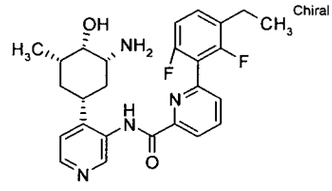
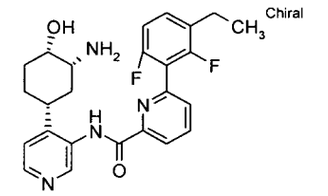
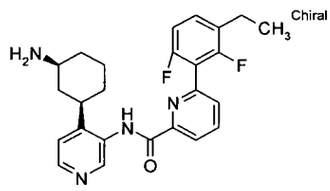
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
1		442.2	0.75	6-(2,6-difluoro-fenil)-5-fluoro-N-(4-((1R,3S,5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-picolinamida
2		474.3	0.52	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-5-fluoro-picolinamida
3		473.3	0.55	3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
4		473.3	0.52	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-5-fluoro-picolinamida

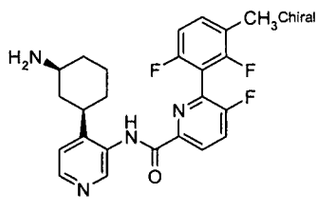
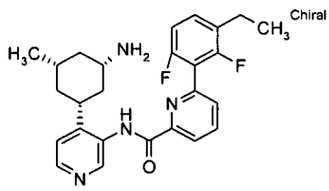
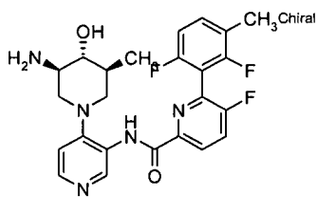
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
5		455.3	0.55	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-hidroxi-fenil)-picolinamida
6		407.2	0.52	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2-fluoro-4-hidroxi-fenil)-picolinamida
7		407.2	0.53	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-hidroxi-fenil)-picolinamida
8		425.2	0.54	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-picolinamida

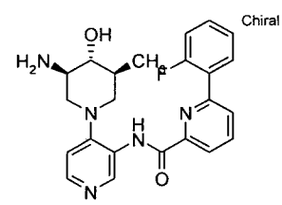
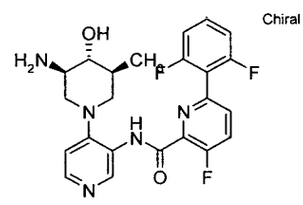
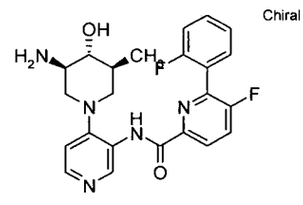
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
9		425.2	0.53	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-4-hidroxi-fenil)-picolinamida
10		453.3	0.58	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-4-hidroxi-fenil)-picolinamida
11		469.2	0.7	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
12		451.1	0.69	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida
13		454.2	0.58	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida
14		445.2	0.62	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-5-fluoro-6-(2,3,5-trifluoro-fenil)-picolinamida

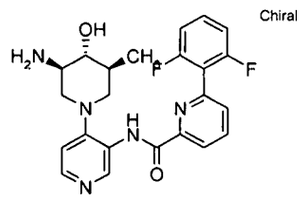
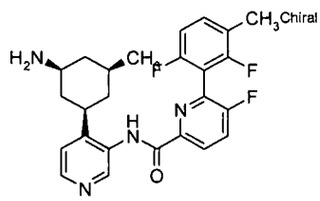
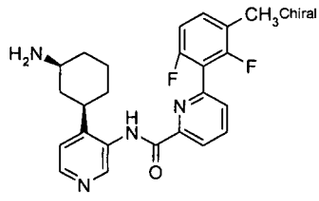
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
15		467.5	0.63	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(3-etil-2,6-difluoro-fenil)-picolinamida
16		428.2	0.63	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-ciclohexil-5-fluoro-picolinamida

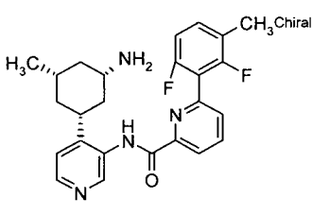
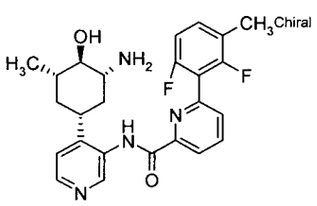
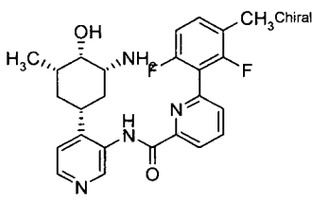
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
17		467.3	0.64	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(3-etil-2,6-difluoro-fenil)-picolinamida
18		453.2	0.66	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(3-etil-2,6-difluoro-fenil)-picolinamida
19		437.2	0.67	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(3-etil-2,6-difluoro-fenil)-picolinamida

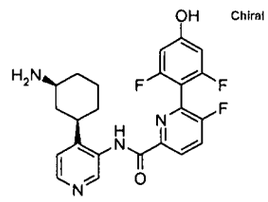
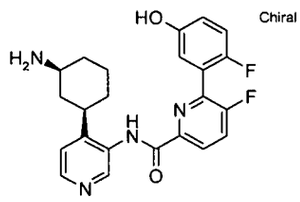
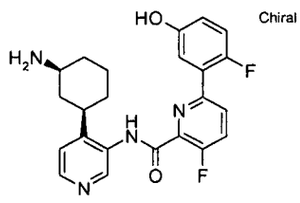
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
20		441.2	0.64	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida
21		451.2	0.7	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(3-etil-2,6-difluoro-fenil)-picolinamida
22		472.3	0.59	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida

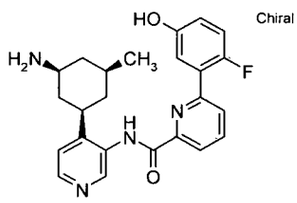
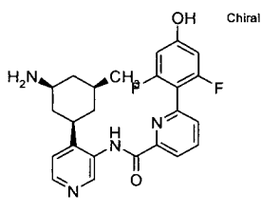
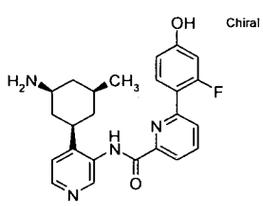
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
23		422.3	0.53	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2-fluoro-fenil)-picolinamida
24		458.3	0.51	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-3-fluoro-picolinamida
25		440.3	0.54	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida

210

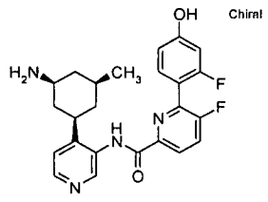
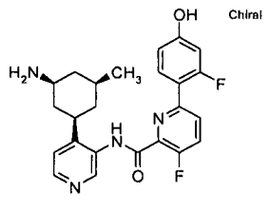
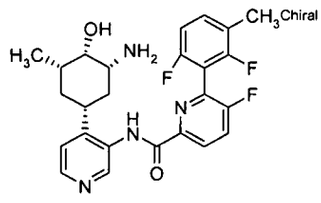
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
26		440.2	0.53	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
27		455.3	0.66	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida
28		423.2	0.61	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida

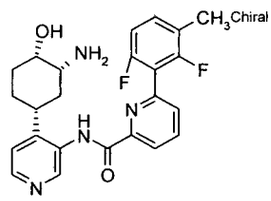
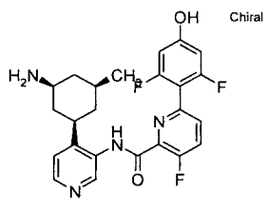
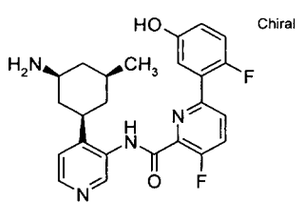
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
29		437.2	0.64	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida
30		453.2	0.59	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida
31		453.2	0.6	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida

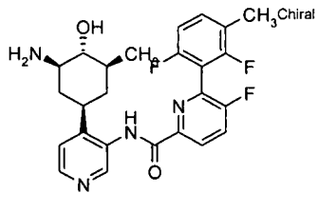
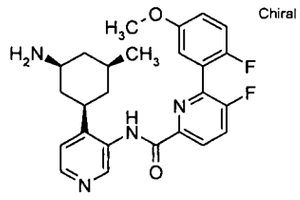
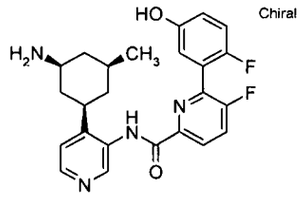
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
32		443.2	0.55	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-5-fluoro-picolinamida
33		425.2	0.53	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-hidroxi-fenil)-picolinamida
34		425.2	0.52	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-3-fluoro-6-(2-fluoro-5-hidroxi-fenil)-picolinamida

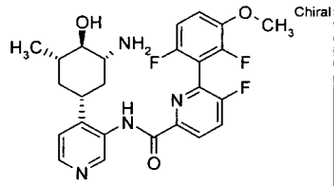
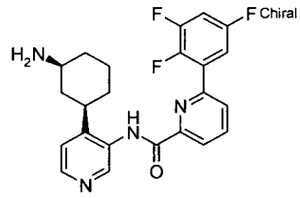
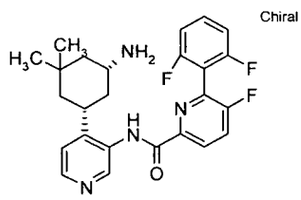
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
35		421.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-hidroxi-fenil)-picolinamida
36		439.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-picolinamida
37		421.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2-fluoro-4-hidroxi-fenil)-picolinamida

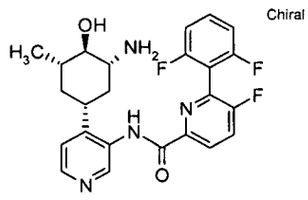
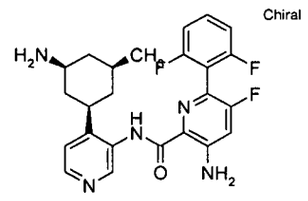
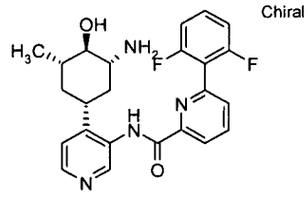
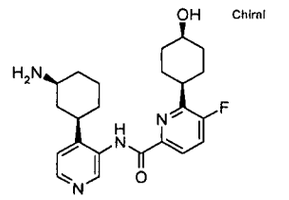
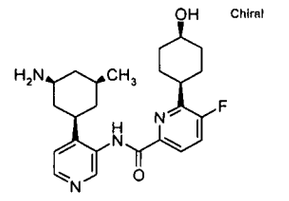
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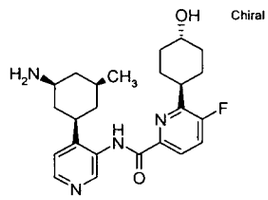
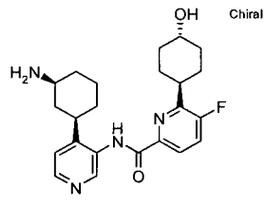
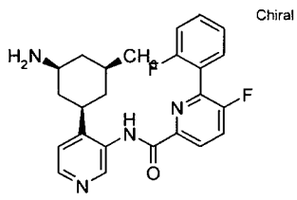
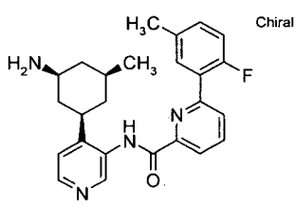
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
38		439.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-4-hidroxi-fenil)-picolinamida
39		439.2	0.55	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-3-fluoro-6-(2-fluoro-4-hidroxi-fenil)-picolinamida
40		471.2	0.62	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
41		439.2	0.57	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-picolinamida
42		457.2	0.56	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-3-fluoro-picolinamida
43		439.2	0.56	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-3-fluoro-6-(2-fluoro-5-hidroxi-fenil)-picolinamida

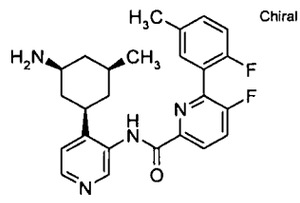
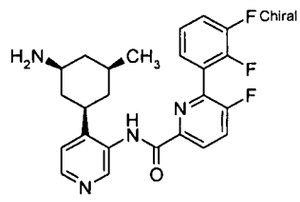
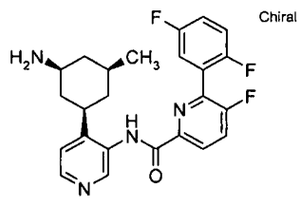
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
44		471.2	0.62	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida
45		453.1	0.61	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-metoxi-fenil)-picolinamida
46		439.1	0.56	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-hidroxi-fenil)-picolinamida

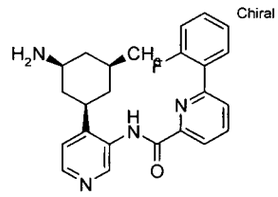
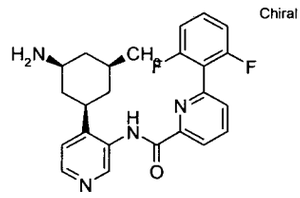
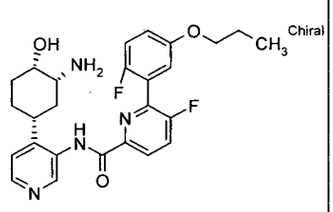
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
47		487.1		N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-metoxi-fenil)-5-fluoro-picolinamida
48		427.2	0.59	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,3,5-trifluoro-fenil)-picolinamida
49		455.2	0.63	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida

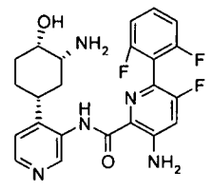
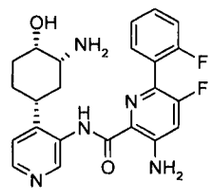
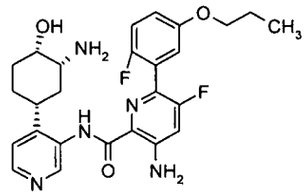
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
50		457.2	0.58	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
51		456.1	0.58	3-amino-N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
52		439.1	0.68	N-(4-((1S,3S,4S,5R)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
53		413.3	0.55	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-5-fluoro-6-((1S,4S)-4-hidroxi-ciclohexil)-picolinamida
54		427.3	0.59	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-((1S,4S)-4-hidroxi-ciclohexil)-picolinamida

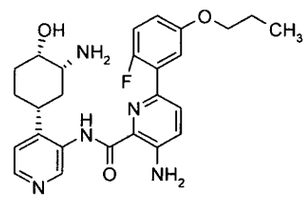
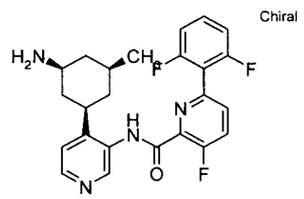
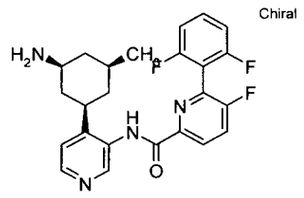
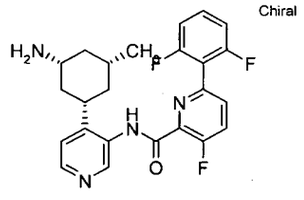
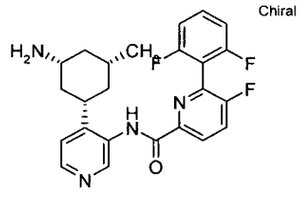
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
55		427.3	0.55	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-((1R,4R)-4-hidroxi-ciclohexil)-picolinamida
56		413.3	0.48	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-5-fluoro-6-((1R,4R)-4-hidroxi-ciclohexil)-picolinamida
57		423.3	0.64	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida
58		419.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-metil-fenil)-picolinamida

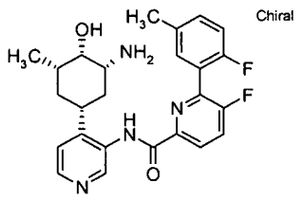
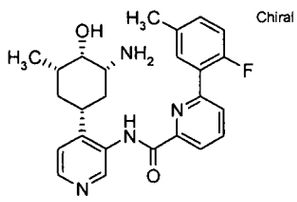
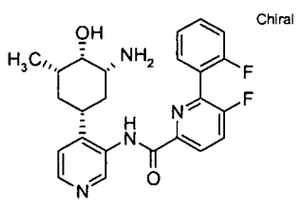
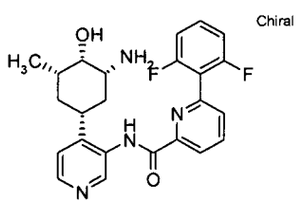
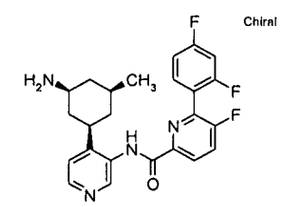
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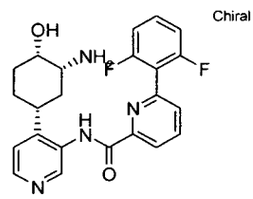
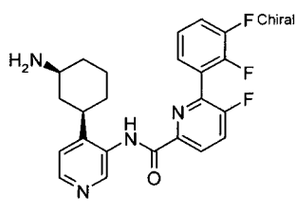
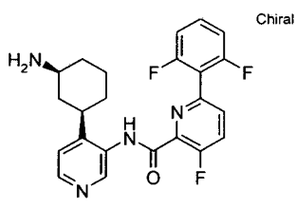
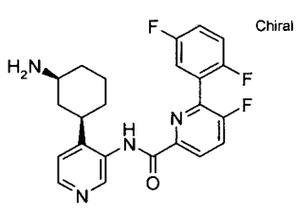
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
59		437.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-metil-fenil)-picolinamida
60		441.2	0.70	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,3-difluoro-fenil)-5-fluoro-picolinamida
61		441.2	0.68	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,5-difluoro-fenil)-5-fluoro-picolinamida

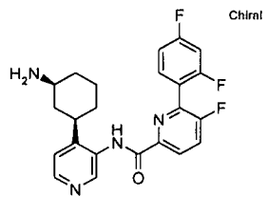
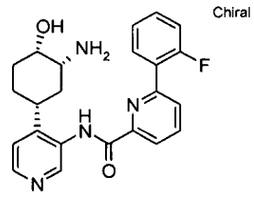
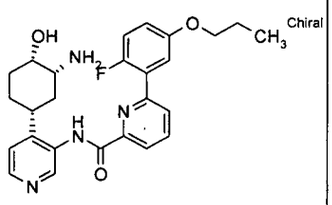
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
62		405.2	0.67	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2-fluoro-fenil)-picolinamida
63		423.2	0.65	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
64		483.2	0.66	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolinamida

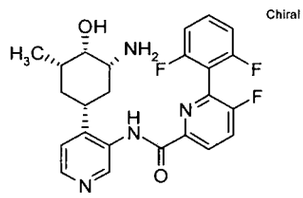
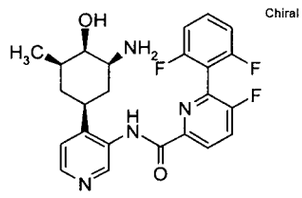
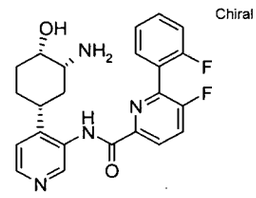
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
65		458.1	0.55	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
66		440.1	0.55	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida
67		498.2	0.66	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-propoxi-fenil)-picolinamida

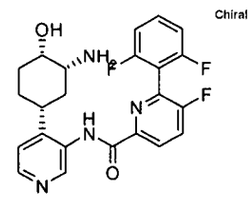
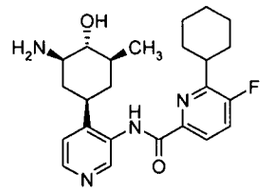
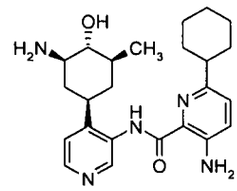
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
68		480.2	0.65	3-amino-N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-propoxi-fenil)-picolinamida
69		441.3	0.67	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-3-fluoro-picolinamida
70		441.3	0.70	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
71		441.3	0.66	N-(4-((1S,3R,5R)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-3-fluoro-picolinamida
72		441.3	0.70	N-(4-((1S,3R,5R)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida

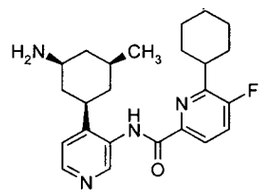
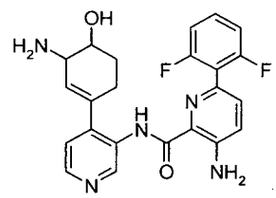
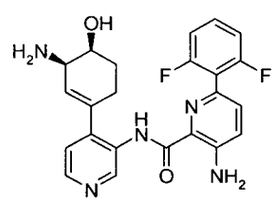
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
73		453.1	0.7	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-metil-fenil)-picolinamida
74		435.0	0.6	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-metil-fenil)-picolinamida
75		439.2	0.57	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida
76		439.2	0.55	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
77		441.3	0.62	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,4-difluoro-fenil)-5-fluoro-picolinamida

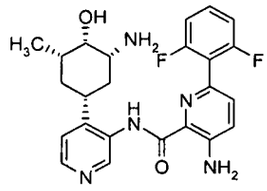
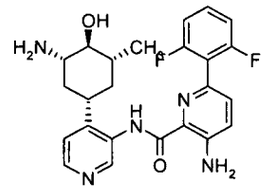
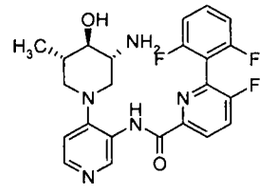
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
78		425.2	0.52	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
79		427.2	0.58	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,3-difluoro-fenil)-5-fluoro-picolinamida
80		427.2	0.54	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-3-fluoro-picolinamida
81		427.2	0.57	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,5-difluoro-fenil)-5-fluoro-picolinamida

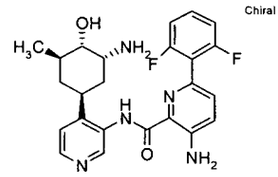
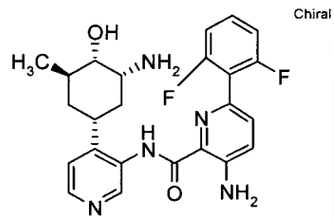
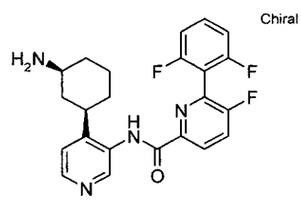
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
82		427.2	0.58	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,4-difluoro-fenil)-5-fluoro-picolinamida
83		407.1	0.51	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2-fluoro-fenil)-picolinamida
84		465.2	0.62	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-propoxi-fenil)-picolinamida

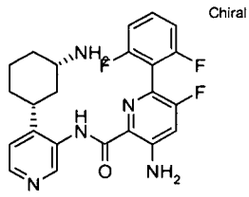
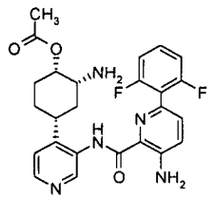
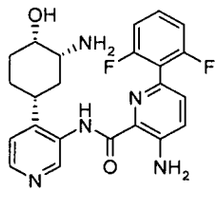
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
85		457.2	0.56	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
86		457.0	0.56	N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
87		425.1	0.52	N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida

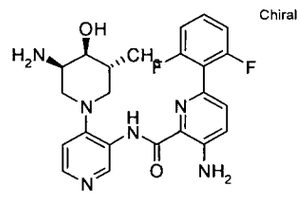
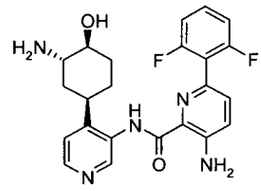
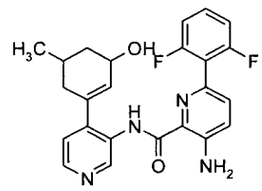
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
88		443.0	0.53	N-(4-((1S,3S,4R)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
89		427.3	0.63	N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-ciclohexil-5-fluoro-picolinamida
90		424.3	0.6	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-ciclohexil-picolinamida

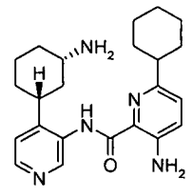
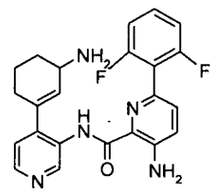
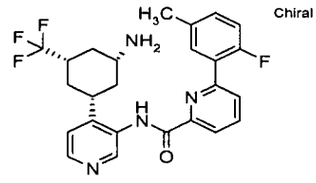
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
91		411.3	0.67	N-(4-(3-amino-5-metil-ciclohexil)-piridin-3-il)-6-ciclohexil-5-fluoro-picolinamida
92		438.3	0.51	3-amino-N-(4-(trans)-3-amino-4-hidroxi-ciclohex-1-enil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
93		438.3	0.51	3-amino-N-(4-(cis)-3-amino-4-hidroxi-ciclohex-1-enil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida

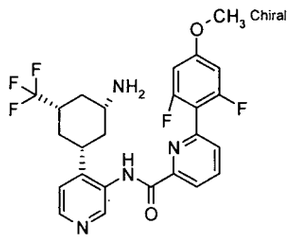
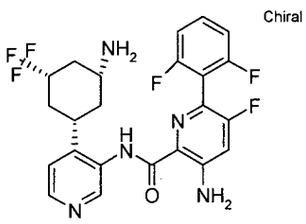
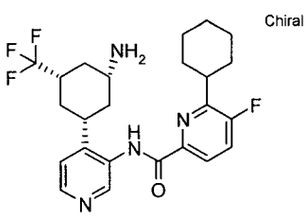
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
94		454.1	0.54	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
95		454.3	0.54	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
96		458.1	0.54	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida

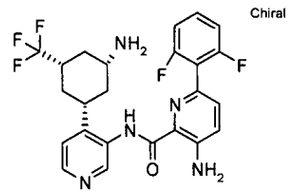
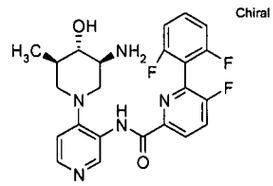
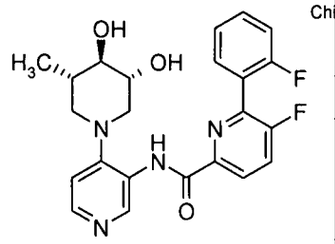
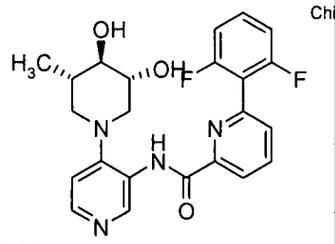
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
97		454.1	0.55	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
98		454.1	0.54	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
99		427.2	0.55	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida

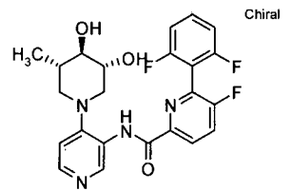
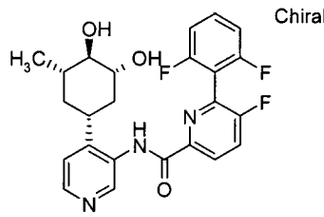
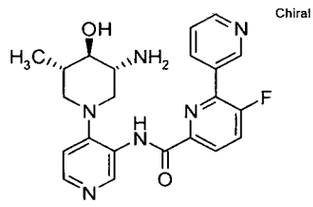
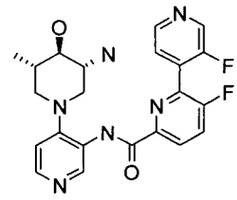
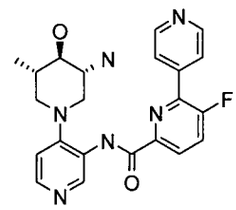
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
100		442.2	0.59	3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
101		482.2	0.56	acetato de 2-amino-4-(3-(3-amino-6-(2,6-difluoro-fenil)-picolinamido)-piridin-4-il)-ciclohexilo
102		440.3	0.52	3-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida

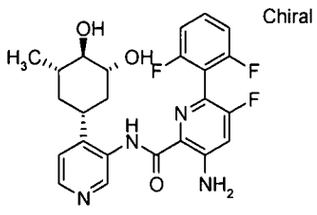
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
103		455.3	0.53	3-amino-N-(4-((3R,4S,5R)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
104		440.2	0.52	3-amino-N-(4-((1R,3S,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
105		438.2	2.92	3-amino-6-(2,6-difluoro-fenil)-N-(4-(3-hidroxi-5-metil-ciclohex-1-enil)-piridin-3-il)-picolinamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
106		394.3	0.74	3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-ciclohexil-picolinamida
107		421.9	0.59	3-amino-N-(4-(3-amino-ciclohex-1-enil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
108		473.3	0.67	N-(4-((1R,3R,5S)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-(2-fluoro-5-metil-fenil)-picolinamida

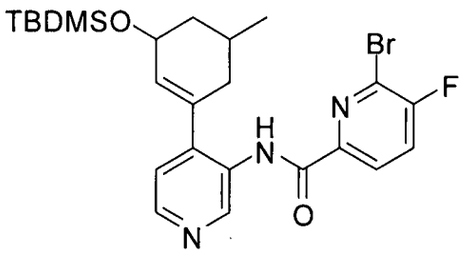
Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
109		507.2	0.65	N-(4-((1R,3R,5S)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-metoxi-fenil)-picolinamida
110		510.2	0.64	3-amino-N-(4-((1R,3R,5S)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
111		465.3	0.72	N-(4-((1R,3R,5S)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-ciclohexil-5-fluoro-picolinamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
112		492.2	0.62	3-amino-N-(4-((1R,3R,5S)-3-amino-5-(trifluoro-metil)-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida
113		458.2	0.55	N-(4-((3S,4S,5R)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
114		441.1	0.61	N-(4-((3R,4R,5S)-3,4-dihidroxi-5-metil-piperidin-1-il)-piridin-3-il)-5-fluoro-6-(2-fluoro-fenil)-picolinamida
115		441.1	0.6	6-(2,6-difluoro-fenil)-N-(4-((3R,4R,5S)-3,4-dihidroxi-5-metil-piperidin-1-il)-piridin-3-il)-picolinamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
116		459.1	0.61	6-(2,6-difluoro-fenil)-N-(4-((3R,4R,5S)-3,4-dihidroxi-5-metil-piperidin-1-il)-piridin-3-il)-5-fluoro-picolinamida
117		458.2	0.62	6-(2,6-difluoro-fenil)-N-(4-((1R,3R,4R,5S)-3,4-dihidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida
118		423.2	0.32	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-3-fluoro-2,3'-bipiridin-6-carboxamida
119		441.2	0.46	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-3,3'-difluoro-2,4'-bipiridin-6-carboxamida
120		423.1	0.3	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-3-fluoro-2,4'-bipiridin-6-carboxamida

Ej. No.	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
121	 Chiral	473.1	0.68	3-amino-6-(2,6-difluoro-fenil)-N-(4-((1R,3R,4R,5S)-3,4-dihidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida

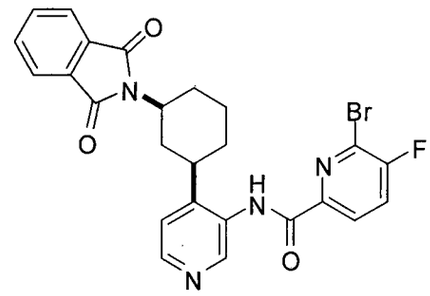
Síntesis de 6-bromo-N-(4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-il)-5-fluoro-picolinamida



Siguiendo el Método 9, la 4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-amina y el ácido 6-bromo-5-fluoro-picolínico se acoplaron, y, en seguida de la adición de EtOAc y el lavado con H_2O, NaCl (saturado), y el secado sobre $MgSO_4$, se obtuvo la 6-bromo-N-(4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-il)-5-fluoro-picolinamida.

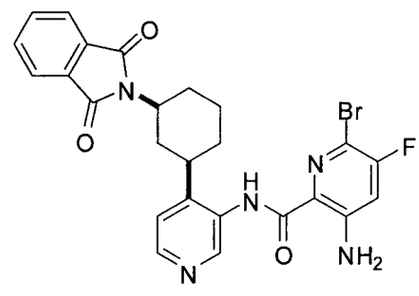
LCMS (*m/z*): 455.3 (MH^+); LC R_t = 2.09 minutos.

Síntesis de 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida



Siguiendo el Método 9, la 2-(3-(3-amino-piridin-4-il)-ciclohexil)-isoindolina-1,3-diona y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl (saturado), y secado sobre $MgSO_4$, se obtuvo la 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida. LCMS (*m/z*): 523.2/525.2 (MH^+); LC R_t = 3.31 minutos.

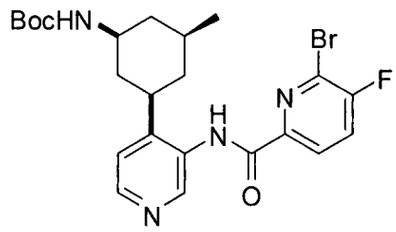
Síntesis de 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida



Siguiendo el Método 9, la 2-(3-(3-amino-piridin-4-il)-ciclohexil)-isoindolina-1,3-diona y el ácido 3-amino-6-bromo-5-

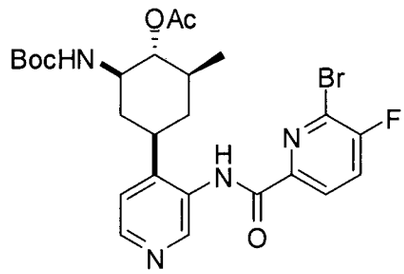
fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl (saturado), y secado sobre $MgSO_4$, se obtuvo la 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida. LCMS (*m/z*): 538.1/540.1 (MH^+); LC R_t = 3.46 minutos.

Síntesis de (1S,3R,5S)-3-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo



Siguiendo el Método 9, el (1S,3R,5S)-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl saturado, y secado sobre $MgSO_4$, se obtuvo el (1S,3R,5S)-3-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo. LCMS (*m/z*): 507.1/509.1 (MH^+), R_t = 0.90 minutos.

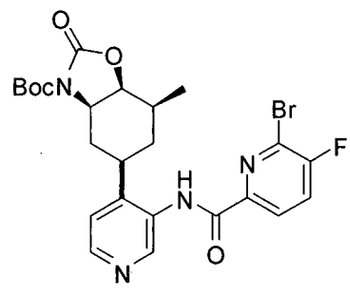
Síntesis de (1R,2R,4R,6S)-acetato de 4-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-2-(ter-butoxi-carbonil-amino)-6-metil-ciclohexilo



Siguiendo el Método 9, el (1R,2R,4R,6S)-acetato de 4-(3-amino-piridin-4-il)-2-(ter-butoxi-carbonil-amino)-6-metil-ciclohexilo y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl (saturado), y secado sobre $MgSO_4$, se obtuvo el (1R,2R,4R,6S)-acetato de 4-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-2-(ter-butoxi-carbonil-amino)-6-metil-ciclohexilo.

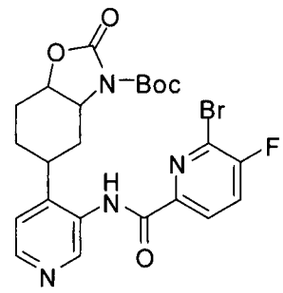
LCMS (*m/z*): 567.2 (MH^+), R_t = 0.82 minutos.

Síntesis de (+/-)-5-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-7-metil-2-oxohexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



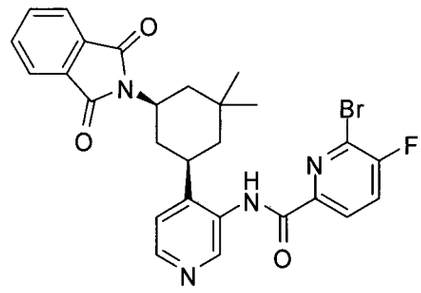
Siguiendo el Método 9, el (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl (saturado), y secado sobre $MgSO_4$, se obtuvo el (+/-)-5-(3-(6-bromo-5-fluoro-picolin-amido)-piridin-4-il)-7-metil-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo. LCMS (*m/z*): 549.2/551.2 (MH^+), R_t = 0.78 minutos.

Síntesis de 5-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo



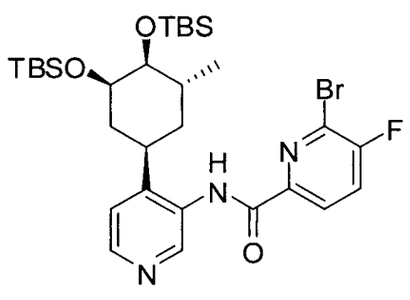
Siguiendo el Método 9, el 5-(3-amino-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl saturado, y secado sobre $MgSO_4$, se obtuvo el 5-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo. LCMS (*m/z*): 537.1 (MH^+); LCMS R_t = 0.71 minutos.

Síntesis de 6-bromo-N-(4-((1R,5R)-5-(1,3-dioxo-isoindolin-2-il)-3,3-dimetil-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida



Siguiendo el Método 9, la 2-((1R,5R)-5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolina-1,3-diona y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl saturado, y secado sobre $MgSO_4$, se obtuvo la 6-bromo-N-(4-((1R,5R)-5-(1,3-dioxo-isoindolin-2-il)-3,3-dimetil-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida. LCMS (*m/z*): 551/553 (MH^+), R_t = 0.95 minutos.

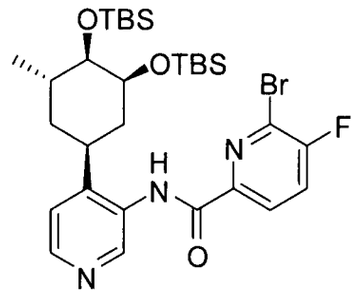
Síntesis de N-(4-((1R,3R,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il)-6-bromo-5-fluoro-picolinamida



Siguiendo el Método 9, la 4-((1R,3R,4S,5R)-3,4-bis-(ter-

butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl saturado, y secado sobre $MgSO_4$, se obtuvo la N-(4-((1R,3R,4S,5R)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il)-6-bromo-5-fluoro-picolinamida. LCMS (*m/z*): 652.5, 652.4 (MH^+); LC R_t = 5.82 minutos.

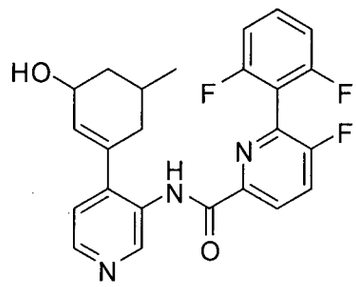
Síntesis de N-(4-((1S,3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il)-6-bromo-5-fluoro-picolinamida



Siguiendo el Método 9, la 4-((1S,3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina y el ácido 6-bromo-5-fluoro-picolínico se acoplaron y, en seguida de la adición de EtOAc y del lavado con H_2O, NaCl saturado, y secado sobre $MgSO_4$, se obtuvo la N-(4-((1S,3S,4R,5S)-3,4-bis-(ter-butil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il)-6-bromo-5-fluoro-picolinamida. LCMS (*m/z*): 652.5, 652.4 (MH^+); LC R_t = 5.83 minutos.

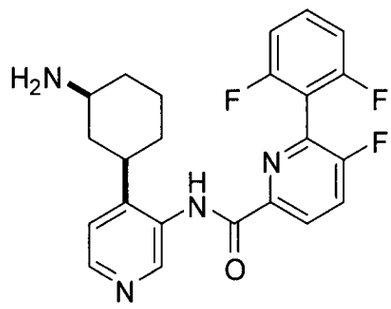
Método 10

Síntesis de 6-(2,6-difluoro-fenil)-5-fluoro-N-(4-(3-hidroxi-5-metil-ciclohex-1-enil)-piridin-3-il)-picolinamida



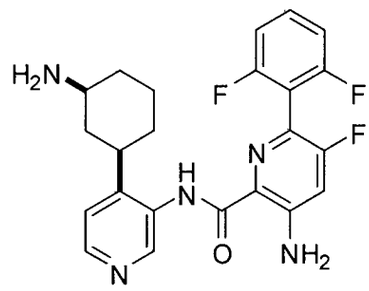
Una solución de la 6-bromo-N-(4-(3-(ter-butil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-piridin-3-il)-5-fluoro-picolinamida (1.0 equivalentes), ácido 2,6-difluoro-fenil-borónico (3.0 equivalentes), tetraquis-trifenil-fosfina (0.2 equivalentes), y trietilamina (3.0 equivalentes) en 1:1 de EtOH/tolueno (0.1 M) se calentó a 120°C con irradiación de microondas durante 1,200 segundos. Después de enfriarse y de remover los volátiles al vacío, el producto de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó, y el éter de TBDMS resultante se desprotegió como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la 6-(2,6-difluoro-fenil)-5-fluoro-N-(4-(3-hidroxi-5-metil-ciclohex-1-enil)-piridin-3-il)-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 438.2 (MH+); LC Rt = 2.00 minutos.

Síntesis de N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida



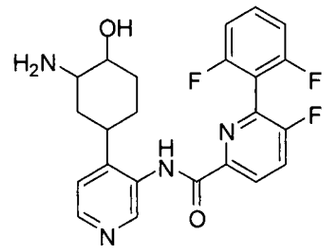
Una solución de la 6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida (1.0 equivalentes), ácido 2,6-difluoro-fenil-borónico (3.0 equivalentes), tetraquis-trifenil-fosfina (0.2 equivalentes), y trietilamina (3.0 equivalentes) en 1:1 de EtOH/tolueno (0.1 M), se calentó a 120°C con irradiación de microondas durante 1,200 segundos. Después de enfriarse y de remover los volátiles al vacío, el producto de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó y el grupo ftalimida resultante se desprotegió como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 427.2 (MH+); LC Rt = 2.26 minutos.

Síntesis de 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida



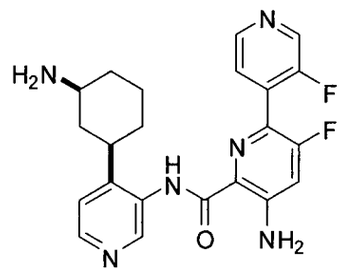
Una solución de la 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida (1.0 equivalentes), ácido 2,6-difluoro-fenil-borónico (3.0 equivalentes), tetraquis-trifenil-fosfina (0.2 equivalentes), y trietilamina (3.0 equivalentes) en 1:1 de EtOH/tolueno (0.1 M), se calentó a 120°C con irradiación de microondas durante 1,200 segundos. Después de enfriarse y de remover los volátiles al vacío, el producto de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó, y el grupo ftalimida resultante se desprotegió como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la 3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 442.2 (MH+); LC Rt = 2.24 minutos.

Síntesis de N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida



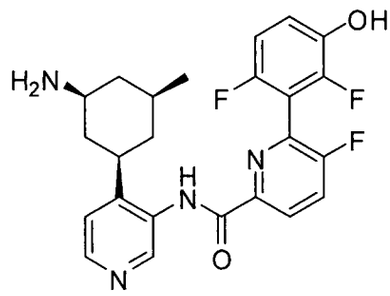
Una solución del 5-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-2-oxo-hexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de ter-butilo (1.0 equivalentes), ácido 2,6-difluoro-fenil-borónico (3.0 equivalentes), tetraquis-trifenil-fosfina (0.2 equivalentes), y trietilamina (3.0 equivalentes) en 1:1 de EtOH/tolueno (0.1 M), se calentó a 120°C con irradiación de microondas durante 1,200 segundos. Después de enfriarse y de remover los volátiles al vacío, el producto de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó, y los grupos carbamato cíclico y Boc resultantes se desprotegieron como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 443.2 (MH+); LC Rt = 2.11 minutos.

Síntesis de 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-3,3'-difluoro-2,4'-bipiridin-6-carboxamida



Una solución de la 3-amino-6-bromo-N-(4-((1R,3S)-3-(1,3-dioxo-isoindolin-2-il)-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida (1.0 equivalentes), ácido 3-fluoro-piridin-4-il-borónico (3.0 equivalentes), tetraquis-trifenil-fosfina (0.2 equivalentes), y trietilamina (3.0 equivalentes) en 1:1 de EtOH/tolueno (0.1 M), se calentó a 120°C con irradiación de microondas durante 1,200 segundos. Después de enfriarse y de remover los volátiles al vacío, el producto de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó, y el grupo ftalimida resultante se desprotegió como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-3,3'-difluoro-2,4'-bipiridin-6-carboxamida como la sal de ácido trifluoro-acético. LCMS (m/z): 425.1 (MH+); LC Rt = 2.08 minutos.

Síntesis de N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinamida

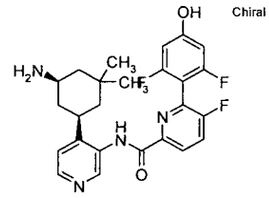
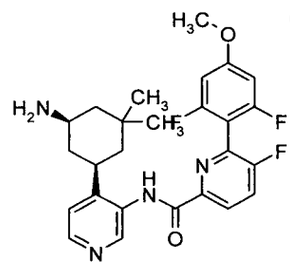


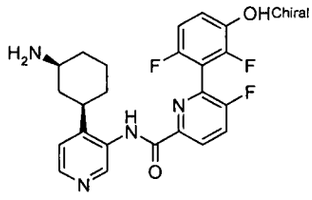
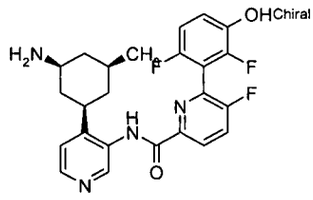
A una solución del (1S,3R,5S)-3-(3-(6-bromo-5-fluoro-picolinamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de ter-butilo (1.0 equivalentes) en un frasco para microondas, se le agregó ácido 2,6-difluoro-3-hidroxi-fenil-borónico (5.0 equivalentes), KF (5.5 equivalentes), y $Pd_2(dba)_3$ (0.2 equivalentes), seguidos por tetrahidrofurano y agua (10:1, 0.03 M). A esta mezcla se le agregó $P(t\text{-}Bu)_3$ (0.4 equivalentes), y la reacción se calentó en el reactor de microondas a 100°C durante 30 minutos. La fase orgánica entonces se separó, la capa acuosa se lavó con acetato de etilo, y los orgánicos se combinaron y se concentraron al vacío. La mezcla cruda se purificó por medio de HPLC de preparación, las fracciones del producto se liofilizaron, y el grupo BOC resultante se desprotegió como se describe en el Método 9, proporcionando, después de la purificación mediante HPLC en fase inversa y de la liofilización, la N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 457.2

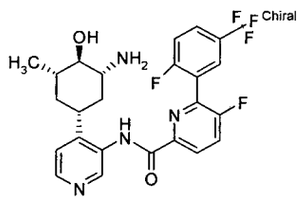
(MH+); LC Rt = 2.17 minutos.

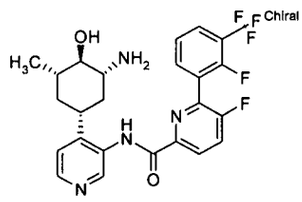
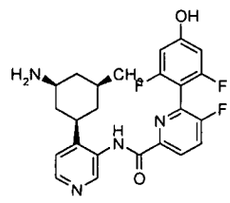
Los siguientes compuestos se prepararon empleando el Método 10:

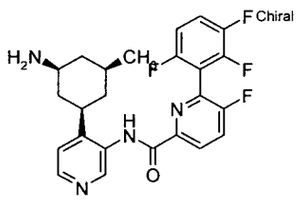
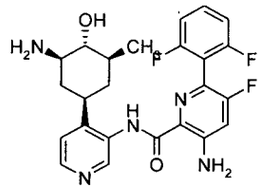
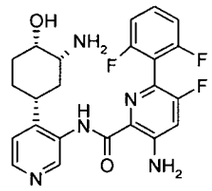
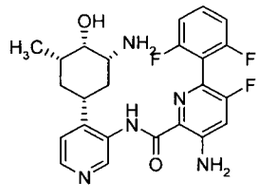
CUADRO 2

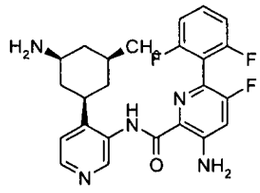
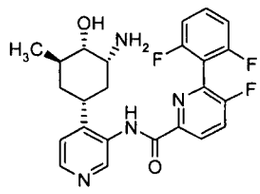
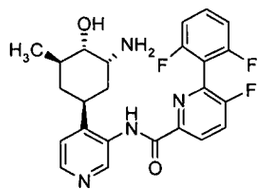
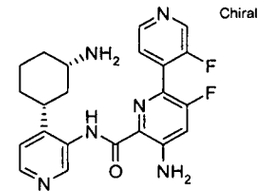
Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
122		471.2	0.58	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-5-fluoro-picolinamida
123		485.2	0.65	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-metoxi-fenil)-5-fluoro-picolinamida

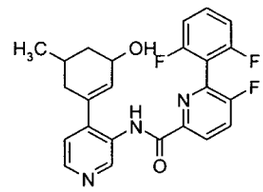
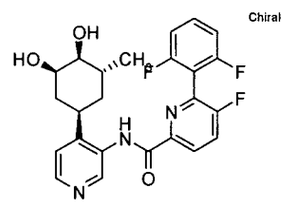
Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
124		443.2	0.54	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinamida
125		457.2	0.57	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-3-hidroxi-fenil)-5-fluoro-picolinamida

Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
126		507.1	0.65	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-5-(trifluoro-metil)-fenil)-picolinamida

Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
127		507.1	0.65	N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2-fluoro-3-(trifluoro-metil)-fenil)-picolinamida
128		457.2	0.58	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-4-hidroxi-fenil)-5-fluoro-picolinamida

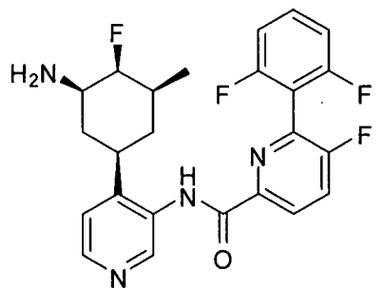
Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
129		459.2	0.62	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-6-(2,3,6-trifluoro-fenil)-picolinamida
130		472.1	0.56	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
131		458.0	0.57	3-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
132		472.1	0.56	3-amino-N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida

Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
133		456.3	0.60	3-amino-N-(4-(3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
134		457.1	0.57	N-(4-(-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
135		457.1	0.55	N-(4-(3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida
136		425.1	0.46	5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-3,3'-difluoro-2,4'-bipiridin-6-carboxamida

Ej. No. / NVP ID	Estructura	LC/MS (M+H en UPCL)	LC/MS (Rf en UPCL)	Nombre Químico
137		440.2	0.75	6-(2,6-difluoro-fenil)-5-fluoro-N-(4-(3-hidroxi-5-metil-ciclohex-1-enil)-piridin-3-il)-picolinamida
138		458.2	0.64	6-(2,6-difluoro-fenil)-N-(4-((1R,3R,4S,5R)-3,4-dihidroxi-5-metil-ciclohexil)-piridin-3-il)-5-fluoro-picolinamida

Ejemplo 139

Síntesis de N-(4-((1R,3R,4S,5S)-3-amino-4-fluoro-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida



A una solución de (1R,2R,3S,5R)-5-(3-(6-(2,6-difluoro-fenil)-5-fluoro-picolinamido)-piridin-4-il)-2-hidroxi-3-metil-ciclohexil-carbamato de ter-butilo (1.0 equivalentes) en dicloro-metano (0.04 M) a 0°C, se le agregó DAST (1.0 equivalentes). La reacción se agitó durante 1.5 horas a 0°C, entonces se agregó ácido trifluoro-acético (10 equivalentes) a la reacción. Después de 2 horas, la reacción se concentró al vacío, y el residuo se purificó por medio de HPLC de preparación, para proporcionar la N-(4-((1R,3R,4S,5S)-3-amino-4-fluoro-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-`difluoro-fenil)-5-fluoro-picolinamida como la sal de ácido trifluoro-acético. LCMS (m/z): 459.3 (MH+); LC Rt = 2.39 minutos.

En adición a la caracterización mediante LC/MS y LC, los compuestos representativos se analizaron mediante ^{1}H-RMN. Los siguientes son los espectros típicos de los compuestos de la invención.

Ej. No.	Datos de ^{1}H-RMN
50	Sal de HCl, ^{1}H-RMN (400 MHz, DMSO-d_6): d 10.54 (bs, 1H), 8.80 (bs, 1H), 8.55 (d, 1H), 8.34 (dd, 1H), 8.20 (t, 1H), 8.00 (bs, 2H), 7.69 (m, 1H), 7.56 (d, 1H), 7.34 (t, 2H), 3.10-3.0 (m, 2H), 2.83 (m, 1H), 2.03 (d, 1H), 1.76-1.59 (m, 2H), 1.40 (m, 1H), 1.31-1.21 (m, 1H), 0.92 (d, 3H).
52	Sal de HCl, ^{1}H-RMN (DMSO-d_6): d 10.4 (s, 1H), 8.71 (s, 1H), 8.37 (d, 1H), 8.14-8.20 (m, 2H), 7.94 (bs, 2H), 7.86-7.88 (m, 2H), 7.54-7.58 (m, 1H), 7.30 (d, 1H), 7.22-7.26 (m, 2H), 2.09-3.02 (m, 2H), 2.78 (m, 1H), 1.96-1.99 (m, 1H), 1.68-1.71 (m, 1H), 1.60 (q, 1H), 1.37 (m, 1H), 1.15-1.24 (m, 1H), 0.88 (d, 3H)
70	Sal de HCl, ^{1}H-RMN (400 MHz, DMSO-d_6): d 10.59 (s, 1H), 8.92 (s, 1H), 8.62 (d, 1H), 8.37 (dd, 1H), 8.23 (t, 1H), 8.19 (bs, 2H), 7.68-7.71 (m, 2H), 7.36-7.40 (m, 2H),3.01-3.10 (m, 2H), 2.01-2.05 (m, 1H), 1.94-1.97 (m, 1H), 1.72-1.76 (m, 1H), 1.46-1.53 (m, 2H), 1.01-1.13 (m, 2H), 0.89 (d, 3H)
85	Sal de HCl, ^{1}H-RMN (DMSO-d_6): d 10.37 (s, 1H), 8.61 (s, 1H), 8.41 (d, 1H), 8.29 (dd, 1H), 8.13 (t, 1H), 7.8 (bs, 2H), 7.69-7.61 (m, 1H), 7.34-7.28 (m, 3H), 3.061 (m, 1H), 2.86 (m, 1H), 1.76-1.63 (m, 2H), 1.53-1.47 (m, 1H), 1.4-1.34 (m, 2H), 0.82 (d, 3H).
88	Sal de HCl, ^{1}H-RMN (DMSO-d_6): d 10.42 (s, 1H), 8.62 (s, 1H), 8.46 (m, 1H), 8.32 (m, 1H), 8.18 (t, 1H), 7.76 (m, 2H), 7.67 (m, 1H), 7.35 (m, 3H), 5.33 (brs, 1H), 3.108 (m, 2H), 2.88 (m, 2H), 1.65 (m, 2H), 1.48 (m, 3H).
96	Sal de HCl, ^{1}H-RMN (400 MHz, CD_3OD): d 9.09 (s, 1 H), 8.46 (dd, 1 H), 8.39 (dd, 1 H), 8.05 (t, 1 H), 7.57 - 7.67 (m, 1 H), 7.53 (d, 1 H), 7.16 - 7.25 (m, 2 H), 4.03 - 4.12 (m, 1 H), 3.85 - 3.94 (m, 1 H), 3.20 (s, 3 H), 2.70 - 2.80 (m, 1 H), 1.67 - 1.79 (m, 1 H), 0.83 (d, 3 H).

Ej. No.	Datos de ^{1}H-RMN
99	Base libre, ^{1}H-RMN ($CDCl_3$): d 9.93(s, 1H), 9.38(s, 1H), 8.40-8.45(m,1H), 8.40(d, 1H), 7.74-7.80(m, 1H), 7.47-7.55(m, 1H), 7.19(d, 1H), 7.06-7.13(m, 2H), 2.68-2.83(m, 2H), 1.97-2.05(m, 1H), 1.65-1.95(m, 5H), 1.22-1.40(m, 3H), 1.04-1.15(m, 1H).
100	Sal de HCl, ^{1}H-RMN (DMSO-d_6): d 10.13(s, 1H), 8.82(s, 1H), 8.41(d, 1H), 7.94(bs, 2H), 7.52-7.62(m, 1H), 7.36(d, 1H), 7.36 (bs, 2H), 7.20-7.31(m, 3H), 2.78-2.88(m, 2H), 1.70-2.02(m, 4H), 1.16-1.54(m, 4H).
102	Sal de HCl, ^{1}H-RMN (400 MHz, DMSO-d_6): d 10.59 (s, 1H), 9.30 (s, 1H), 8.54 (d, 1H) 8.08 (br s, 3H), 7.75 (d, 1H), 7.65 (d, 1H), 7.60–7.56 (m, 1H), 7.49 (d, 1H), 7.33 (t, 2H), 4.04 (br s, 1H), 3.16(br s, 2H) 3.05 (br t, 1H), 1.98–1.20 (m, 7H)
116	Sal de HCl, ^{1}H-RMN (400, d_6-DMSO): d 10.47 (s, 1H), 8.56 (s, 1H), 8.33 (dd, 1H), 8.26 (dd, 1H), 8.20 (t, 1H), 7.62-7.72 (m, 1H), 7.30-7.35 (m, 3H), 3.82-3.92 (m, 2H), 3.18-3.22 (m, 1H), 2.84-2.91 (m, 1H), 2.69 (t, J=13.2, 1H), 1.38-1.46 (m, 1H), 0.69 (d, 3H).
128	Sal de HCl, ^{1}H-RMN (400, d_6-DMSO): d 11.00 (s, 1H), 10.46 (s, 1H), 8.55 (d, 1H), 8.29 (dd, 1H), 8.15 (t, 1H), 8.05 (bs, 2H), 7.54 (d, 1H), 6.72 (d, 2H), 3.04 - 3.10 (m, 1H), 2.92-3.04 (m, 1H), 2.01 (d, 1H), 1.95 (d, 1H), 1.74 (d, 1H), 1.42-1.52 (m, 2H), 0.97-1.08 (m, 2 H), 0.88 (d, 3H).

Ejemplo 140

Ensayo de agotamiento de ATP de Pim1

Se mide la actividad de PIM1 utilizando un reactivo de

detección de ATP basado en luciferina de luciferasa, para cuantificar el agotamiento de ATP resultante de la transferencia de fosforilo catalizada por cinasa hasta un sustrato peptídico. Los compuestos que se van a probar se disuelven en sulfóxido de dimetilo al 100 por ciento, y se distribuyen directamente en placas blancas de 384 cavidades a 0.5 microlitros por cavidad. Para iniciar la reacción, se agregan a cada cavidad 10 microlitros de cinasa Pim1 5 nM y péptido BAD 80 µM (RSRHSSYPAGT-OH) en regulador de ensayo (HEPES 50 mM, pH de 7.5, $MgCl_2$ 5 mM, y DTT 1 mM, albúmina de suero bovino al 0.05 por ciento). Después de 15 minutos, se agregan 10 microlitros de ATP 40 µM en regulador de ensayo. Las concentraciones finales del ensayo son: PIM1 2.5 nM, ATP 20 µM, péptido BAD 40 µM, y sulfóxido de dimetilo al 2.5 por ciento. La reacción se lleva a cabo hasta que se agota aproximadamente el 50 por ciento del ATP, entonces se detiene con la adición de 20 microlitros de solución KinaseGlo Plus (Promega Corporation). La reacción detenida se incuba durante 10 minutos, y el ATP restante se detecta por medio de luminiscencia en el Victor2 (Perkin Elmer). Los compuestos de los ejemplos anteriores se probaron mediante el ensayo de agotamiento de ATP de Pim1, y se encontró que exhiben valores IC_{50} como se muestran en el Cuadro 3 que se encuentra más adelante. La IC_{50}, la concentración inhibidora media máxima, representa la concentración de un compuesto de

prueba que se requiere para la inhibición del 50 por ciento de su objetivo *in vitro*.

Ejemplo 141

Ensayo de agotamiento de ATP de Pim2

La actividad de PIM2 se mide utilizando un reactivo de detección de ATP basado en luciferina de luciferasa, para cuantificar el agotamiento de ATP resultante de la transferencia de fosforilo catalizada por cinasa hacia un sustrato peptídico. Los compuestos que se van a probar se disuelven en sulfóxido de dimetilo al 100 por ciento, y se distribuyen directamente en placas blancas de 384 cavidades, a 0.5 microlitros por cavidad. Para iniciar la reacción, se agregan a cada cavidad 10 microlitros de cinasa Pim2 10 nM y péptido BAD 20 µM (RSRHSSYPAGT-OH) en regulador de ensayo (HEPES 50 mM, pH de 7.5, $MgCl_2$ 5 mM, y DTT 1 mM, albúmina de suero bovino al 0.05 por ciento). Después de 15 minutos, se agregan 10 microlitros de ATP 8 µM en regulador de ensayo. Las concentraciones finales del ensayo son: PIM2 5 nM, ATP 4 µM, péptido BAD 10 µM, y sulfóxido de dimetilo al 2.5 por ciento. La reacción se lleva a cabo hasta que se agota aproximadamente el 50 por ciento del ATP, entonces se detiene con la adición de 20 microlitros de solución KinaseGlo Plus (Promega Corporation). La reacción detenida se incuba durante 10 minutos, y el ATP restante se detecta por medio de

luminiscencia en el Victor2 (Perkin Elmer). Los compuestos de los ejemplos anteriores se probaron mediante el ensayo de agotamiento de ATP de Pim2, y se encontró que exhiben valores IC_{50} como se muestran en el Cuadro 3 que se encuentra más adelante.

Ejemplo 142

Ensayo de agotamiento de ATP de Pim3

La actividad de PIM3 se mide utilizando un reactivo de detección de ATP basado en luciferina de luciferasa, para cuantificar el agotamiento de ATP resultante de la transferencia de fosforilo catalizada por cinasa hacia un sustrato peptídico. Los compuestos que se van a probar se disuelven en sulfóxido de dimetilo al 100 por ciento, y se distribuyen directamente en placas blancas de 384 cavidades, a 0.5 microlitros por cavidad. Para iniciar la reacción, se agregan a cada cavidad 10 microlitros de cinasa Pim3 10 nM y péptido BAD 20 µM (RSRHSSYPAGT-OH) en regulador de ensayo (HEPES 50 mM, pH de 7.5, $MgCl_2$ 5 mM, y DTT 1 mM, albúmina de suero bovino al 0.05 por ciento). Después de 15 minutos, se agregan 10 microlitros de ATP 8 µM en regulador de ensayo. Las concentraciones finales del ensayo son: PIM3 5 nM, ATP 4 µM, péptido BAD 100 µM, y sulfóxido de dimetilo al 2.5 por ciento. La reacción se lleva a cabo hasta que se agota aproximadamente el 50 por ciento del ATP, entonces se detiene

con la adición de 20 microlitros de solución KinaseGlo Plus (Promega Corporation). La reacción detenida se incuba durante 10 minutos, y el ATP restante se detecta por medio de luminiscencia en el Victor2 (Perkin Elmer). Los compuestos de los ejemplos anteriores se probaron mediante el ensayo de agotamiento de ATP de Pim3, y se encontró que exhiben valores IC_{50} como se muestran en el Cuadro 3 que se encuentra más adelante.

Ejemplo 143

Ensayo de Proliferación Celular

Se cultivaron células KMS11 (línea celular de mieloma humano) en IMDM complementado con suero bovino fetal al 10 por ciento, piruvato de sodio, y antibióticos. Las células se aplicaron en el mismo medio a una densidad de 2,000 células por cavidad en placas de cultivo de tejido de 96 cavidades, con las cavidades externas vacías, en el día del ensayo. Se cultivaron células MM1.s (línea celular de mieloma humano) en RPMI1640 complementado con suero bovino fetal al 10 por ciento, piruvato de sodio, y antibióticos. Las células se aplicaron en el mismo medio a una densidad de 5,000 células por cavidad en placas de cultivo de tejido de 96 cavidades, con las cavidades externas vacías, en el día del ensayo.

Los compuestos de prueba suministrados en sulfóxido de dimetilo se diluyeron en sulfóxido de dimetilo a 500 veces las

concentraciones finales deseadas antes de la dilución en el medio de cultivo, hasta 2 veces las concentraciones finales. Se agregaron volúmenes iguales de los compuestos de prueba 2 veces a las células en placas de 96 cavidades, y se incubaron a 37°C durante 3 días.

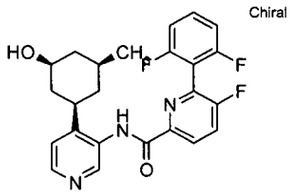
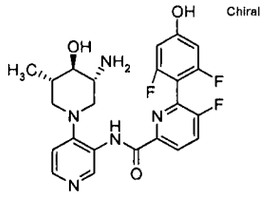
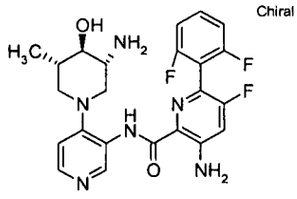
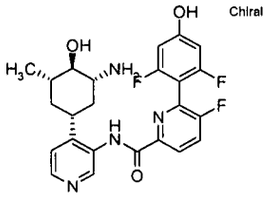
Después de 3 días, las placas se equilibraron a temperatura ambiente, y se agregó un volumen igual de Reactivo Cell Titer-Glow (Promega) a las cavidades de cultivo. Las placas se agitaron brevemente, y la señal luminiscente se midió con el luminómetro. Se calculó el porcentaje de inhibición de la señal que se ve en las células tratadas con sulfóxido de dimetilo solamente contra las células tratadas con el compuesto de control, y se utilizó para determinar los valores EC_{50} (es decir, la concentración de un compuesto de prueba que se requiere para obtener el 50 por ciento del máximo efecto en las células) para los compuestos probados, como se muestra en el Cuadro 3.

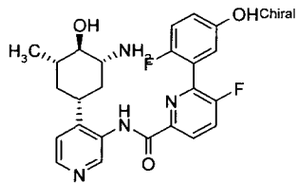
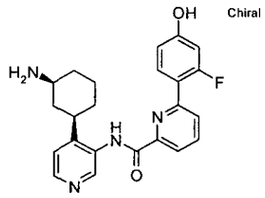
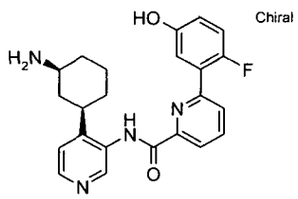
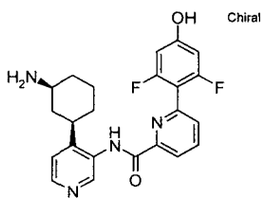
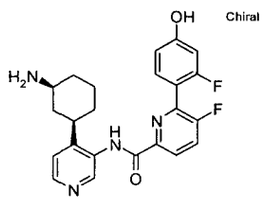
Empleando los procedimientos de los Ejemplos 140 (ensayo de agotamiento de ATP de Pim 1), 141 (ensayo de agotamiento de ATP de Pim 2), y 142 (ensayo de agotamiento de ATP de Pim 3), se determinó la concentración IC_{50} de los compuestos de los ejemplos anteriores, como se muestra en el siguiente Cuadro 3.

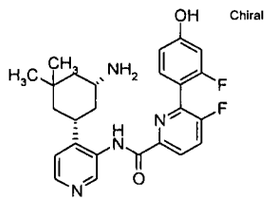
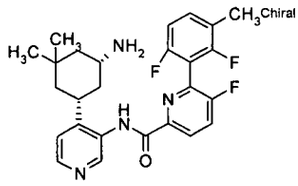
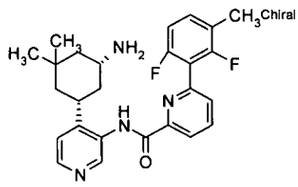
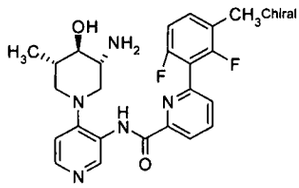
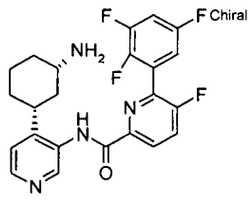
Empleando los procedimientos del Ejemplo 143 (ensayo de proliferación celular), se determinó la concentración EC_{50} de

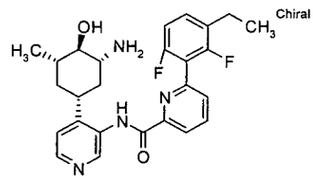
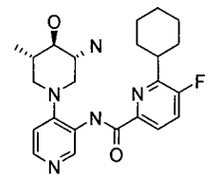
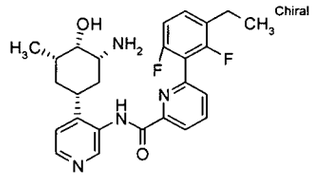
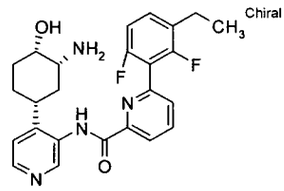
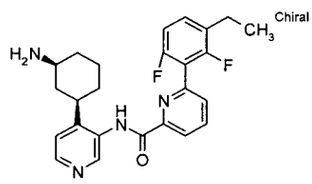
los compuestos de los ejemplos en células KMS11, como se muestra en el Cuadro 3.

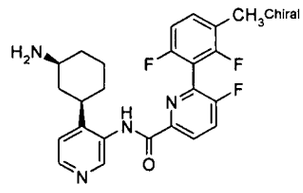
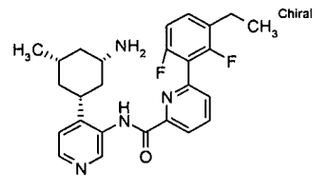
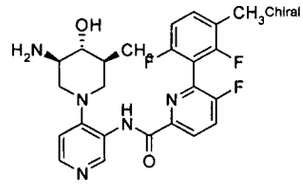
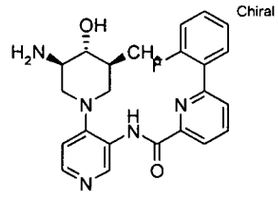
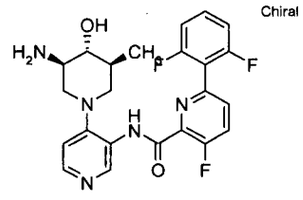
CUADRO 3

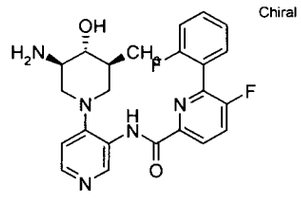
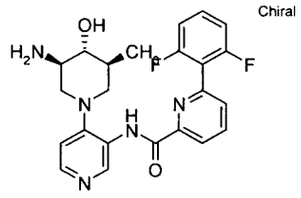
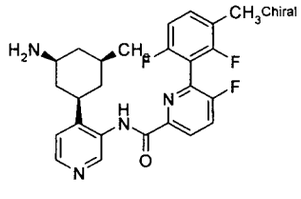
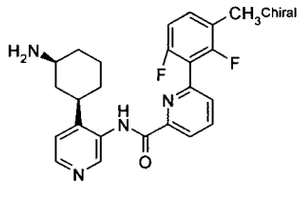
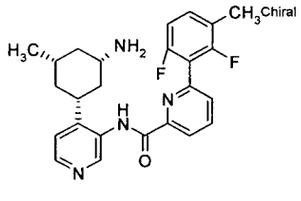
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
1		0.001	0.018	0.006	7.6
2		0.001	0.001	0.001	0.07
3		0.001	0.001	0.001	0.01
4		0.001	0.003	0.002	1.3

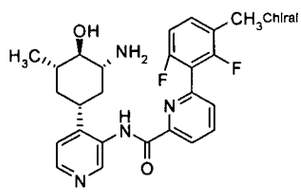
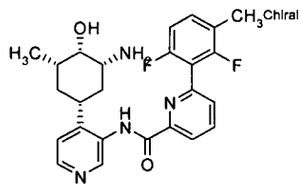
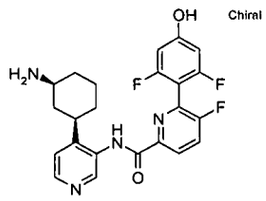
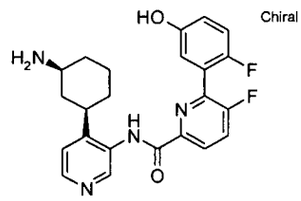
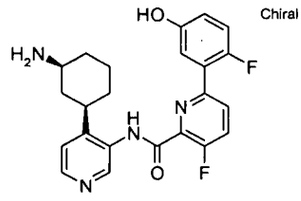
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
5		0.003	0.020	0.009	4.8
6		0.002	0.012	0.003	4.1
7		0.001	0.008	0.002	0.33
8		0.001	0.004	0.002	0.51
9		0.001	0.008	0.002	1.6

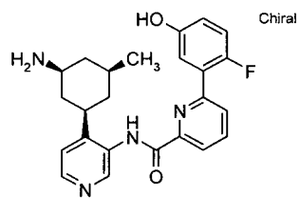
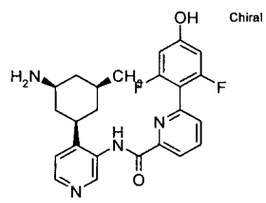
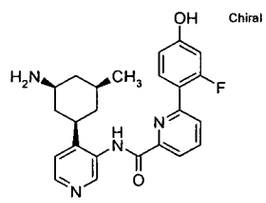
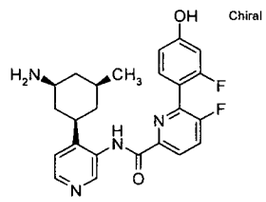
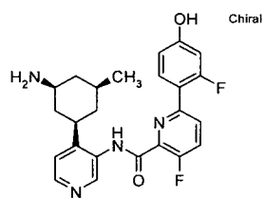
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
10		0.001	0.012	0.006	2.9
11		0.001	0.005	0.004	2.6
12		0.001	0.010	0.004	2.4
13		0.001	0.004	0.003	0.67
14		0.006	0.040	0.012	8.5

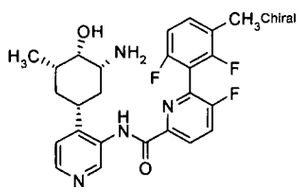
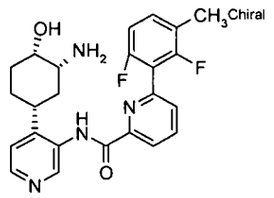
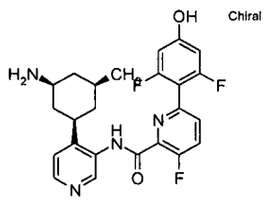
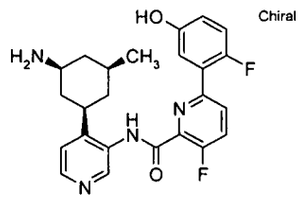
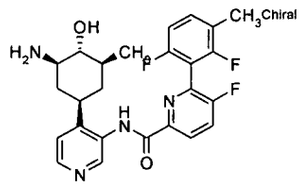
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
15		0.003	0.027	0.006	5.5
16		0.001	0.003	0.003	1.7
17		0.001	0.013	0.005	3.5
18		0.003	0.062	0.007	6.3
19		0.003	0.054	0.007	4.5

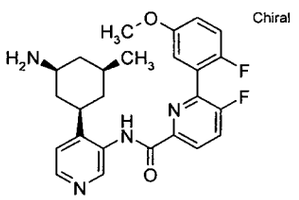
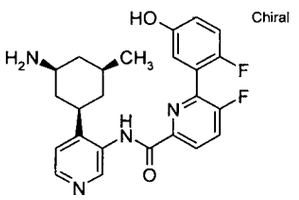
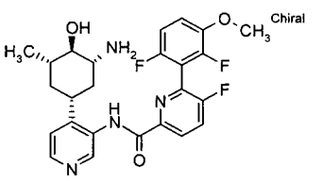
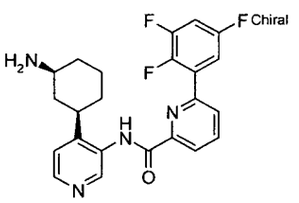
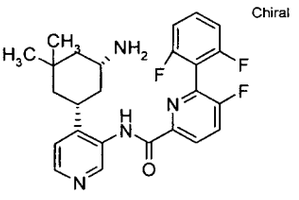
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
20		0.001	0.007	0.003	1.5
21		0.002	0.013	0.006	3.3
22		0.001	0.002	0.003	0.21
23		0.002	0.005	0.003	1.9
24		0.001	0.002	0.001	0.62

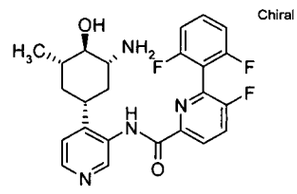
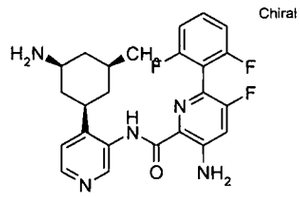
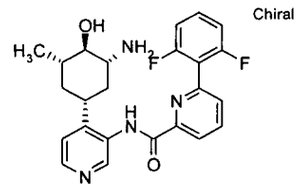
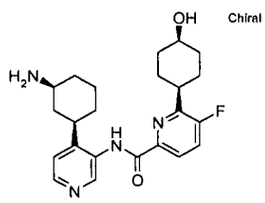
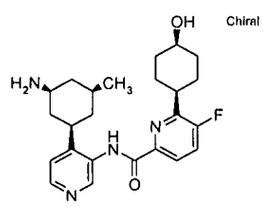
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
25		0.001	0.002	0.002	0.37
26		0.001	0.002	0.002	0.29
27		0.001	0.003	0.002	0.95
28		0.001	0.011	0.002	2.2
29		0.001	0.004	0.003	1.4

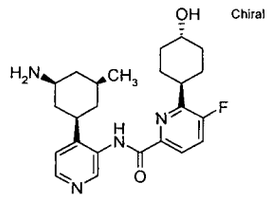
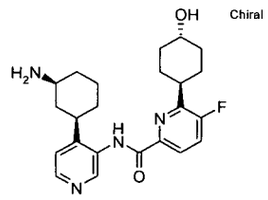
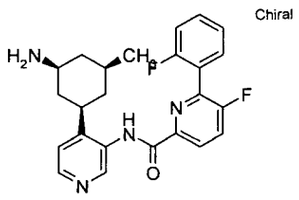
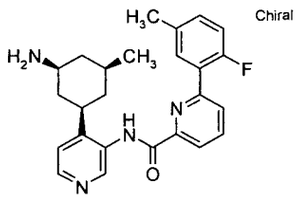
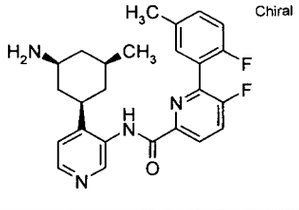
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
30		0.002	0.012	0.004	2.1
31		0.002	0.007	0.004	1.1
32		0.001	0.004	0.003	0.39
33		0.001	0.009	0.003	1.4
34		0.004	0.067	0.006	6.0

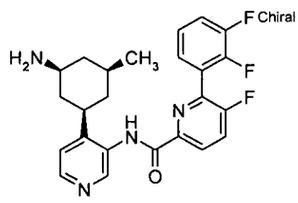
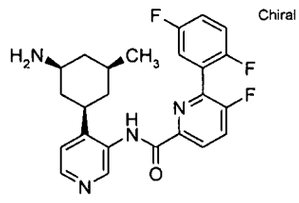
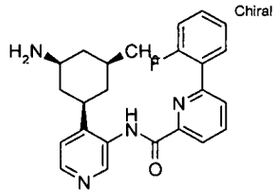
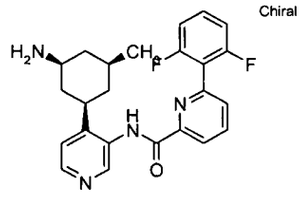
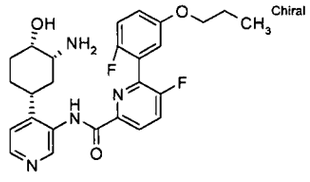
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
35	 Chiral	0.001	0.006	0.003	0.67
36	 Chiral	0.001	0.003	0.003	0.24
37	 Chiral	0.002	0.007	0.005	1.5
38	 Chiral	0.001	0.004	0.003	0.73
39	 Chiral	0.007	0.028	0.012	6.6

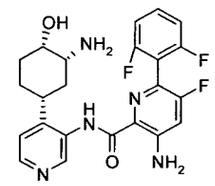
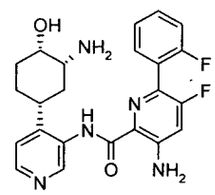
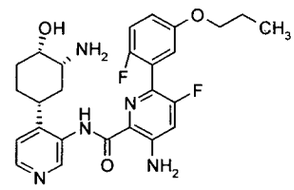
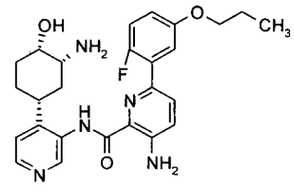
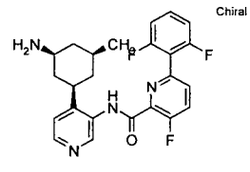
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
40		0.001	0.003	0.002	0.99
41		0.002	0.027	0.005	2.0
42		0.001	0.002	0.002	3.0
43		0.001	0.006	0.002	2.2
44		0.001	0.002	0.002	1.9

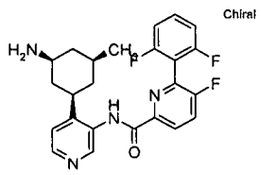
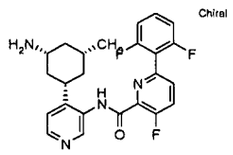
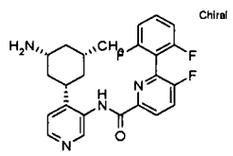
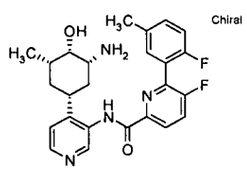
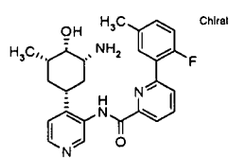
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
45		0.001	0.002	0.002	1.3
46		0.001	0.002	0.002	0.76
47		0.001	0.004	0.003	1.3
48		0.007	0.076	0.009	
49		0.001	0.003	0.002	1.8

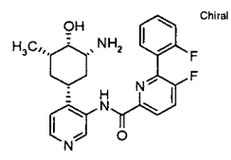
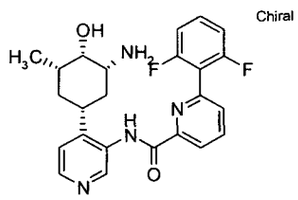
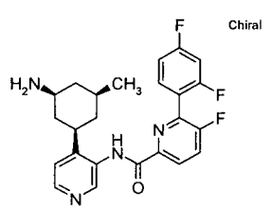
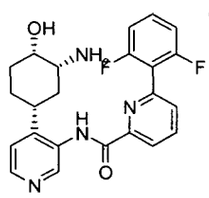
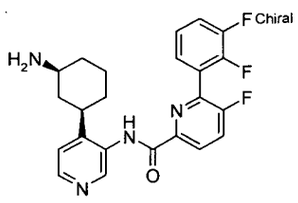
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
50		0.001	0.003	0.002	1.2
51		0.001	0.002	0.001	0.31
52		0.001	0.003	0.002	0.83
53		0.010	0.149	0.065	>10
54		0.003	0.026	0.024	3.8

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
55		0.003	0.011	0.030	4.9
56		0.011	0.081	0.102	>10
57		0.001	0.004	0.002	1.4
58		0.001	0.008	0.003	1.8
59		0.001	0.003	0.002	1.1

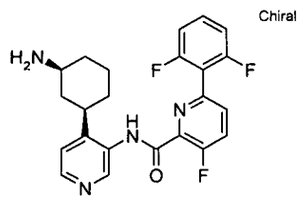
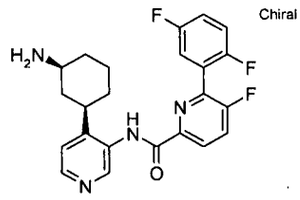
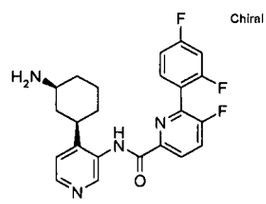
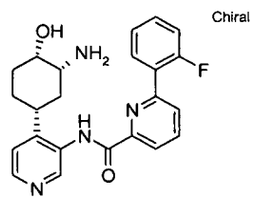
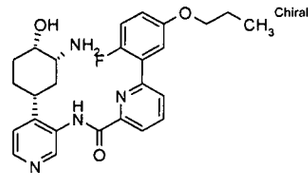
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
60		0.001	0.005	0.003	1.3
61		0.001	0.006	0.004	1.2
62		0.001	0.007	0.003	2.4
63		0.001	0.003	0.002	0.53
64		0.002	0.076	0.005	5.6

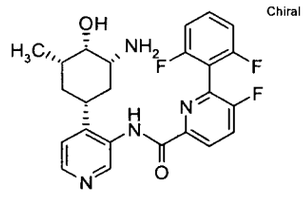
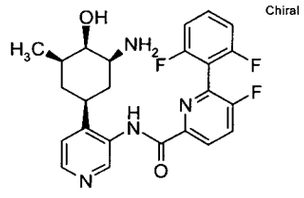
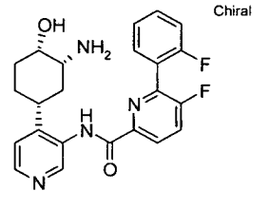
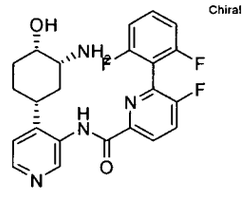
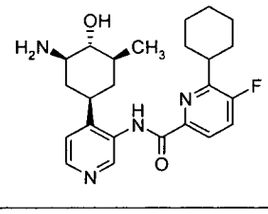
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
65		0.001	0.004	0.003	0.16
66		0.001	0.004	0.002	0.52
67		0.001	0.007	0.003	1.2
68		0.001	0.008	0.004	1.4
69		0.003	0.007	0.006	1.0

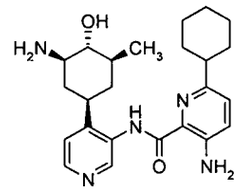
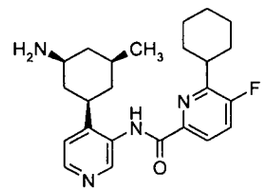
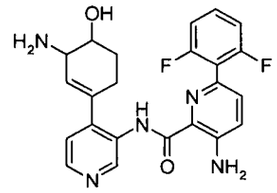
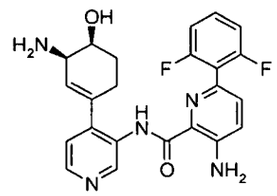
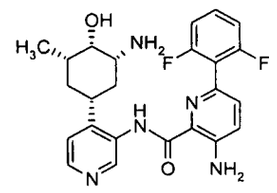
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
70		0.001	0.002	0.002	0.48
71		0.662	1.947	1.05	
72		0.095	0.522	0.369	
73		0.001	0.008	0.004	1.4
74		0.001	0.017	0.004	2.9

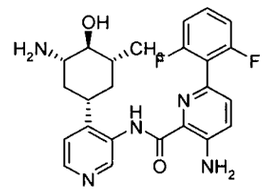
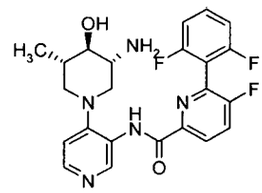
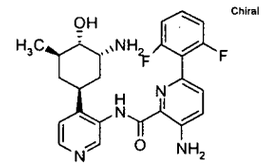
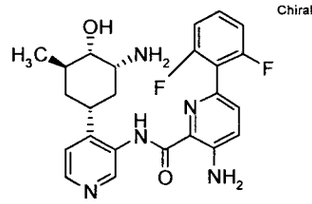
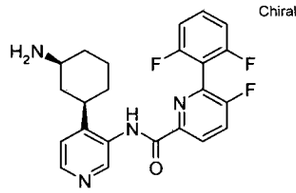
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
75		0.001	0.008	0.003	2.1
76		0.001	0.003	0.002	0.83
77		0.001	0.013	0.003	3.9
78		0.002	0.015	0.003	3.6
79		0.002	0.020	0.003	4.6

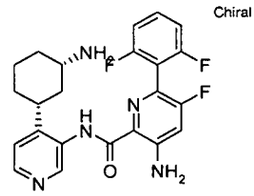
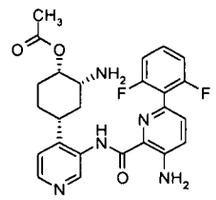
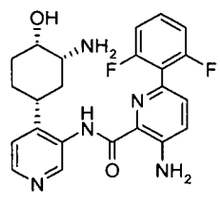
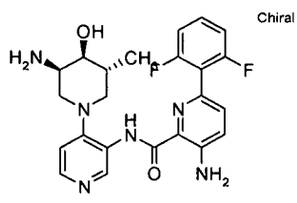
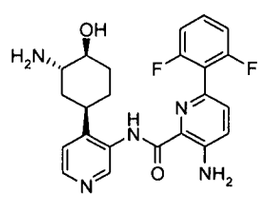
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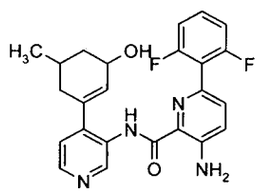
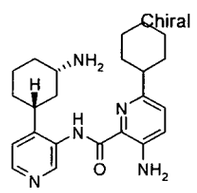
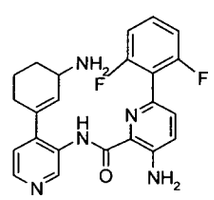
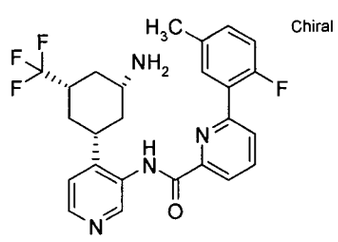
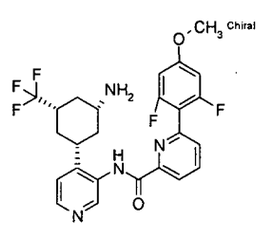
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
80		0.006	0.044	0.007	7.9
81		0.002	0.025	0.005	5.940
82		0.003	0.080	0.009	>10
83		0.004	0.048	0.005	>10
84		0.004	0.163	0.007	6.9

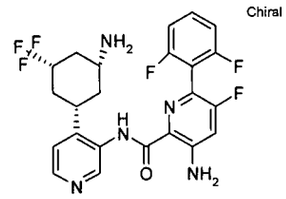
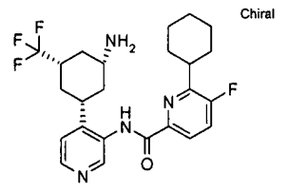
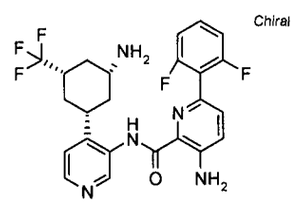
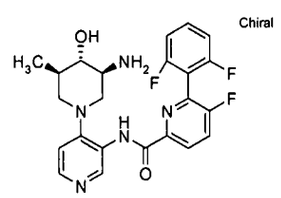
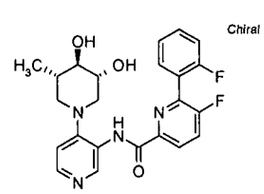
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
85		0.001	0.003	0.002	0.41
86		0.031	0.124	0.106	6.1
87		0.002	0.035	0.005	7.7
88		0.001	0.011	0.005	0.79
89		0.008	0.021	0.029	

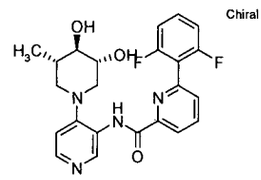
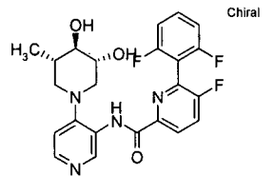
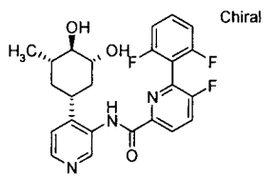
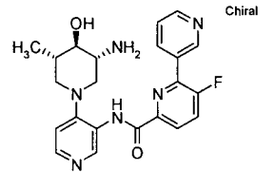
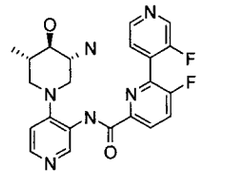
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
90		0.003	0.010	0.012	
91		0.003	0.012	0.021	2.9
92		0.002	0.009	0.005	
93		0.001	0.008	0.005	
94		0.001	0.003	0.005	0.239

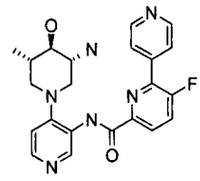
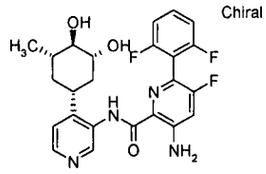
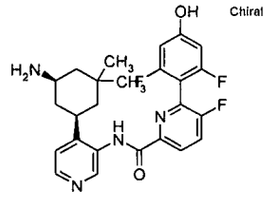
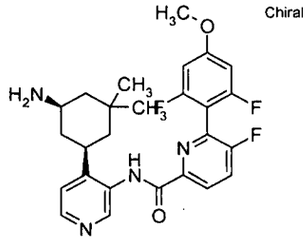
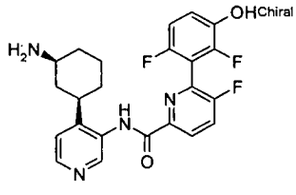
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
95		0.001	0.005	0.006	0.537
96		0.001	0.001	0.001	0.03
97		0.002	0.010	0.007	3.3
98		0.002	0.005	0.005	0.81
99		0.001	0.005	0.003	0.93

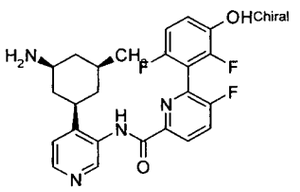
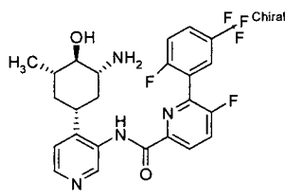
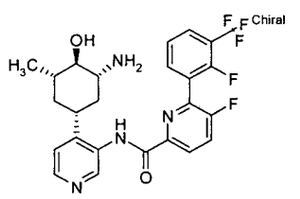
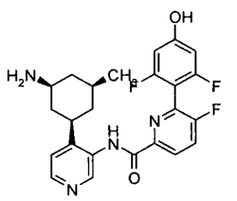
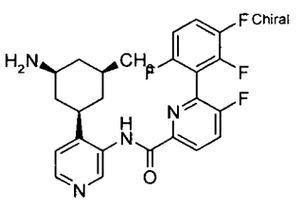
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
100		0.001	0.001	0.001	0.28
101		0.002	0.007	0.005	
102		0.001	0.004	0.004	0.87
103		0.002	0.008	0.004	
104		0.003	0.013	0.005	

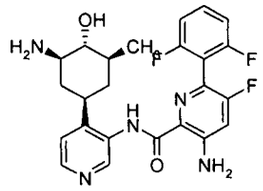
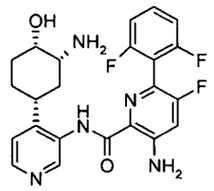
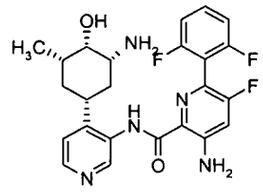
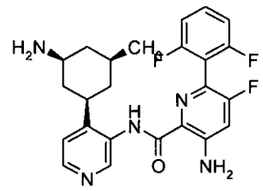
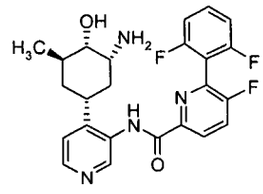
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
105		0.001	0.006	0.004	
106		0.005	0.022	0.014	
107		0.002	0.007	0.006	0.93
108		0.001	0.007	0.003	
109		0.001	0.002	0.002	

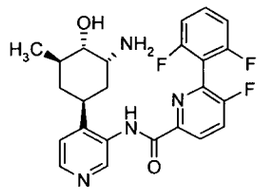
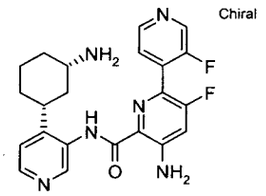
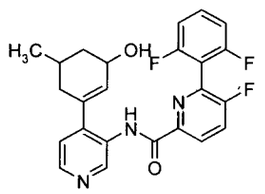
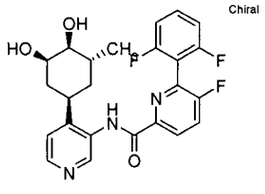
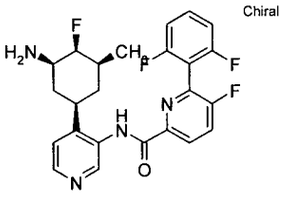
Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
110		0.001	0.001	0.001	
111		0.002	0.005	0.011	
112		0.001	0.001	0.001	
113		0.004	0.089	0.028	
114		0.001	0.003	0.001	0.64

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
115		0.001	0.002	0.001	0.59
116		0.001	0.001	0.001	0.29
117		0.001	0.006	0.002	2.5
118		0.004	0.029	0.009	4.6
119		0.001	0.004	0.002	1.2

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
120		0.003	0.018	0.007	8.5
121	 Chiral	0.001	0.001	0.002	
122	 Chiral	0.001	0.002	0.002	0.23
123	 Chiral	0.001	0.004	0.002	0.49
124	 Chiral	0.001	0.002	0.001	0.78

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
125		0.001	0.001	0.001	0.41
126		0.002	0.068	0.017	
127		0.011	0.131	0.027	
128		0.001	0.001	0.001	0.26
129		0.001	0.003	0.002	1.2

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
130		0.002	0.007	0.008	1.0
131		0.002	0.007	0.006	0.43
132		0.001	0.005	0.006	0.38
133		0.001	0.004	0.007	0.24
134		0.002	0.016	0.008	1.9

Ej. No./ NVP ID	Estructura	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11-luc EC_{50} µM
135		0.023	0.088	0.036	
136		0.002	0.024	0.009	6.4
137		0.001	0.020	0.007	
138		0.002	0.045	0.006	
139		0.001	0.005	0.004	1.9

Ejemplo 144

Método Biológico: Estudio de Modulación y Eficacia de Objetivo de Farmacología en Modelo de Xenoinjerto de Mieloma Múltiple

Las células de cáncer de mieloma múltiple KMS11-luc, obtenidas de Suzanne Trudel (University Health Network, Toronto, Canadá), expresan la luciferasa estable, logrado mediante transfección retroviral, y se mantuvieron en DMEM complementado con suero bovino fetal inactivado por calor al 10 por ciento, con glutamina al 1 por ciento (Invitrogen, Inc.). Se utilizaron ratones SCID/bg hembras (de 8 a 12 semanas de edad, de 20 a 25 gramos, Charles River) para todos los estudios de farmacología *in vivo*. Los ratones se alojaron y se mantuvieron de acuerdo con los lineamientos estatales y federales para el tratamiento y cuidado humanitario de los animales de laboratorio, y recibieron alimento y agua al gusto. Las células de cáncer se cosecharon a partir de los cultivos en fase de registro medio, se estableció el conteo de células viables con un contador de células automatizado (Vi-CELL, Beckman-Coulter), y las células se volvieron a suspender en partes iguales de HBSS y Matrigel (Invitrogen, Inc.). Se inyectaron diez millones de células subcutáneamente en el flanco derecho de cada ratón. El tratamiento con el compuesto se inició cuando el tamaño del tumor alcanzó de 250 a 350 milímetros cúbicos para los estudios de

farmacocinética/farmacodinamia, y de 150 a 250 milímetros cúbicos para los estudios de eficacia, determinándose los volúmenes tumorales utilizando el software StudyDirector (StudyLog Systems, Inc.). Todos los compuestos del tratamiento se administraron oralmente.

Para la modulación del objetivo *in vivo* en los estudios en el transcurso del tiempo de farmacocinética/farmacodinamia, a los ratones que tenían tumor se les administró una sola dosis oral de vehículo o del compuesto en diferentes concentraciones. A las 1, 8, y 24 horas después de la dosificación, se tomaron muestras de los tejidos tumorales y de sangre a partir de los ratones individuales. Los tejidos tumorales reseccionados se congelaron instantáneamente y se pulverizaron utilizando un criomortero y pistilo enfriado con nitrógeno líquido. Las muestras de sangre se tomaron mediante punción cardíaca, y se separó el plasma utilizando tubos de centrifugación que contenían heparina de litio y separador de plasma (BD Microtainer). Las muestras tumorales congeladas se lisaron en regulador frío (Meso Scale Discovery) complementado con inhibidor de proteasa libre de EDTA (Roche), inhibidores de fosfatasa 1 y 2, y NaF 1M (Sigma) de acuerdo con las instrucciones del fabricante. En seguida de la homogeneización con un aparato Dounce o mediante el MagNA Lyser (Roche), se obtuvo un sobrenadante transparente en seguida de la centrifugación a 300xg durante 30 minutos a 4°C,

y se determinó la concentración de proteína mediante BCA (BioRad). La modulación del objetivo se determinó utilizando el kit dúplex Meso Scale fosfo-Bad^{SeR112}/total Bad, de acuerdo con las instrucciones del fabricante. Dicho de una manera breve, se cargó una cantidad igual de proteína en cada cavidad de una placa dúplex de 96 cavidades Meso Scale fosfo-Serina^{112}/total Bad (Meso Scale Discovery), y las muestras se incubaron durante 30 minutos a temperatura ambiente o durante la noche a 4°C, con agitación. Las placas se lavaron con regulador de lavado MSD 1x, y se agregó el anticuerpo de detección Sulfo-Tag a las cavidades, y se incubaron durante 1 hora a temperatura ambiente, con agitación. Las placas se lavaron nuevamente, y se capturó el analito detectado en seguida de la adición del Regulador de Lectura T a las cavidades. Las placas se leyeron en un Instrumento SECTOR Imager 6000 (Meso Scale Discovery). Se utilizaron las proporciones de la señal a partir de pBad a Bad total, para corregir la variabilidad entre las muestras. Los datos mostrados en el siguiente cuadro expresan el porcentaje de inhibición de la fosforilación de pBad^{SeR112} en relación con la fosforilación de Bad total mediante los compuestos representativos de la invención, normalizado con el grupo de control de vehículo. El grado de modulación se expresa como un porcentaje en relación con el control de vehículo (*n.d.*, no determinado).

Compuesto del Ejemplo No.	1 hora	8 horas	24 horas
99 (50 miligramos/kilogramo)	40	55	0
99 (100 miligramos/kilogramo)	62	66	24
70 (25 miligramos/kilogramo)	34	50	*n.d.*
70 (50 miligramos/kilogramo)	28	62	0
70 (100 miligramos/kilogramo)	5	67	68
96 (25 miligramos/kilogramo)	0	24	*n.d.*
96 (50 miligramos/kilogramo)	44	69	16
96(100 miligramos/kilogramo)	58	71	53

Para los estudios de eficacia, los ratones que tenían tumor se seleccionaron aleatoriamente en grupos con una variación equivalente del volumen tumoral en el intervalo de 150 a 250 milímetros cúbicos, utilizando el software StudyDirector (StudyLog Systems, Inc.). En seguida de la selección aleatoria, los ratones se dosificaron oralmente una o dos veces al día en múltiples concentraciones del compuesto, en incipiente de 200 microlitros. Se midieron el crecimiento de los tumores y el peso corporal de los animales cuando menos dos veces por semana, y se utilizaron observaciones clínicas diarias para verificar las toxicidades potenciales relacionadas

con el tratamiento. Los animales se removieron del estudio si el volumen tumoral excedía de 2,500 milímetros cúbicos, o si la pérdida de peso corporal excedía del 20 por ciento de las mediciones iniciales.

Se evaluó la eficacia del Ejemplo 99 en el modelo de xeno-injerto KMS11-luc, recibiendo los ratones la administración oral del compuesto del Ejemplo 99 dos veces al día en 50 y 100 miligramos/kilogramo, y una vez al día en 100 miligramos/kilogramo durante 14 días. La dosificación se inició cuando los tamaños de los tumores alcanzaron aproximadamente 250 milímetros cúbicos. Como se muestra en la Figura 1, el compuesto del Ejemplo 99 exhibió efectos dependientes de la dosis *in vivo*, observándose la inhibición del crecimiento tumoral con 50 miligramos/kilogramo dos veces al día (92 por ciento), y 100 miligramos/kilogramo dos veces al día (regresión del 4 por ciento). La administración una vez al día de 100 miligramos/kilogramo fue menos eficaz (65 por ciento) que cuando se dosificó dos veces al día. Estos resultados se correlacionan con la extensión y magnitud de modulación de $pBad^{SeR112}$, y sugieren que se requiere de una modulación de objetivo extensa y prolongada para una máxima eficacia.

Se evaluó la eficacia del compuesto del Ejemplo 70 en el modelo de xeno-injerto KMS11-luc, recibiendo los ratones la administración oral del compuesto del Ejemplo 80 dos veces al

día en 25 y 50 miligramos/kilogramo, y una vez al día en 100 miligramos/kilogramo durante 14 días. La dosificación se inició cuando los tamaños de los tumores alcanzaron aproximadamente 225 milímetros cúbicos. Como se muestra en la Figura 2, el compuesto del Ejemplo 70 exhibió efectos dependientes de la dosis *in vivo*, observándose la inhibición del crecimiento tumoral con 25 miligramos/kilogramo (65 por ciento), y 50 miligramos/kilogramo (100 por ciento). También se observó una inhibición significativa del crecimiento tumoral con 100 miligramos/kilogramo una vez al día (84 por ciento).

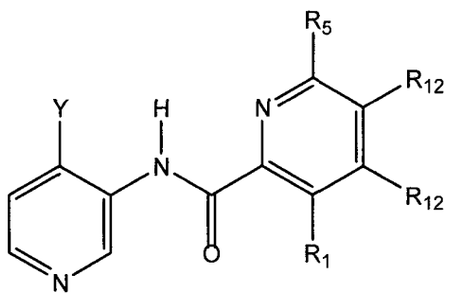
Se evaluó la eficacia del compuesto del Ejemplo 96 en el modelo de xeno-injerto KMS11-luc, recibiendo los ratones la administración oral del compuesto del Ejemplo 96 dos veces al día en 25 y 50 miligramos/kilogramo, y una vez al día en 100 miligramos/kilogramo durante 14 días. La dosificación se inició cuando los tamaños de los tumores alcanzaron aproximadamente 225 milímetros cúbicos. Como se muestra en la Figura 3, el compuesto del Ejemplo 96 exhibió efectos dependientes de la dosis *in vivo*, observándose la inhibición del crecimiento tumoral con 25 miligramos/kilogramo (67 por ciento), y con 50 miligramos/kilogramo (96 por ciento). También se observó una inhibición significativa del crecimiento tumoral con 100 miligramos/kilogramo una vez al día (88 por ciento).

Aunque se ha ilustrado y descrito la modalidad preferida de la invención, se apreciará que se pueden hacer diferentes

cambios en la misma sin apartarse del espíritu y alcance de la invención.

REIVINDICACIONES

1. Un compuesto de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



II

en donde:

Y es ciclohexilo sustituido con uno a tres sustituyentes;

R_1 es hidrógeno, $-NH_2$, o halógeno;

R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno y halógeno; y

R_5 se selecciona a partir de ciclohexilo, fenilo, y piridilo, en donde este ciclohexilo, este fenilo, y este piridilo están cada uno independientemente sustituidos con hasta tres sustituyentes seleccionados a partir de halógeno, hidroxilo, alquilo de 1 a 4 átomos de carbono, y O-alquilo de 1 a 4 átomos de carbono.

2. Un compuesto de la reivindicación 1, en donde Y está sustituido con uno a tres sustituyentes seleccionados a partir de hidroxilo, amino, alquilo de 1 a 4 átomos de carbono, y halo-alquilo de 1 a 4 átomos de carbono.

3. Un compuesto de la reivindicación 2, en donde Y está sustituido con uno a tres sustituyentes seleccionados a partir de metilo, hidroxilo, amino, y CF_3.

4. Un compuesto de la reivindicación 2, en donde R_1 es hidrógeno, amino, o flúor.

5. Un compuesto de la reivindicación 2, en donde R_5 es piridilo o fenilo.

6. Un compuesto de la reivindicación 5, en donde R_5 es fenilo sustituido con hasta tres sustituyentes seleccionados a partir de halógeno, hidroxilo, alcoxilo, y alquilo de 1 a 4 átomos de carbono.

7. Un compuesto de la reivindicación 5, en donde Y está sustituido con uno a tres sustituyentes seleccionados a partir de metilo, hidroxilo, amino, y CF_3; R_1 es hidrógeno; y R_5 es fenilo sustituido con hasta tres sustituyentes seleccionados a partir de flúor, hidroxilo, metilo, etilo, metoxilo, y propoxilo.

8. Un compuesto de la reivindicación 7, en donde R_1 es 2,6-difluoro-fenilo.

9. Un compuesto de la reivindicación 1, seleccionado a partir del grupo que consiste en:

N-(4-((3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida;

3-amino-N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-picolinamida;

N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-

piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida;

3-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida; y

N-(4-((3S)-3-amino-ciclohexil)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de las mismas.

10. Una composición farmacéutica, la cual comprende un compuesto de cualquiera de la reivindicación 1 a la reivindicación 9.

11. Una composición farmacéutica, la cual comprende un compuesto de cualquiera de la reivindicación 1 a la reivindicación 9, en donde esta composición farmacéutica comprende un agente adicional para el tratamiento de cáncer.

12. Una composición farmacéutica de la reivindicación 11, en donde el agente adicional se selecciona a partir de irinotecano, topotecano, gemcitabina, 5-fluoro-uracilo, leucovorina, carboplatina, cisplatina, taxanos, tezacitabina, ciclofosfamida, alcaloides vinca, imatinib (Gleevec), antraciclinas, rituximab, y trastuzumab.

13. Un uso de un compuesto de cualquiera de la reivindicación 1 a la reivindicación 9, para la preparación de un medicamento para el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM).

14. El uso de la reivindicación 13, en donde la condición

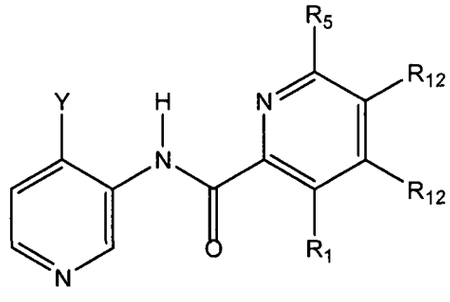
es un cáncer seleccionado a partir de carcinoma de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon, melanoma, leucemia mieloide, mieloma múltiple, y eritroleucemia, adenoma de colon velloso, y osteosarcoma.

15. Un compuesto de las reivindicaciones 1 a 9, para utilizarse en el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM).

16. El compuesto de la reivindicación 15, en donde la condición es un cáncer seleccionado a partir de carcinoma de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon, melanoma, leucemia mieloide, mieloma múltiple, y eritroleucemia, adenoma de colon velloso, y osteosarcoma.

17. Un compuesto de la fórmula II, seleccionado a partir del Cuadro I o del Cuadro II.

18. Un compuesto de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



II

en donde:

Y es piperidinilo sustituido con metilo, hidroxilo, y amino;

R_1 se selecciona a partir del grupo que consiste en hidrógeno, NH_2, y flúor;

R_{12}, independientemente en cada presentación, se selecciona a partir del grupo que consiste en hidrógeno y halógeno; y

R_5 se selecciona a partir de piridilo, fluoro-piridilo, ciclohexilo, y fenilo, en donde el fenilo está sustituido con hasta tres sustituyentes seleccionados a partir de flúor, hidroxilo, y metilo.

19. Un compuesto de la reivindicación 18, en donde Y representa 3-amino-4-hidroxi-5-metil-piperidin-1-ilo.

20. Un compuesto de la reivindicación 18 ó 19, en donde R_1 es hidrógeno.

21. Un compuesto de la reivindicación 20, en donde R_5 es difluoro-fenilo.

22. Un compuesto de la reivindicación 18 o de la reivindicación 19, en donde R_5 es 2,6-difluoro-fenilo.

23. Un compuesto de la reivindicación 18, seleccionado a partir de N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, 3-amino-N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-fenil)-5-fluoro-picolinamida, y N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-6-(2,6-difluoro-3-metil-fenil)-5-fluoro-picolinamida.

24. Una composición farmacéutica, la cual comprende un compuesto de la reivindicación 18 o de la reivindicación 23, en donde esta composición farmacéutica comprende cuando menos un agente adicional para el tratamiento de cáncer.

25. La composición farmacéutica de la reivindicación 24, en donde el agente adicional se selecciona a partir del grupo que consiste en irinotecano, topotecano, gemcitabina, 5-fluoro-uracilo, leucovorina, carboplatina, cisplatina, taxanos, tezacitabina, ciclofosfamida, alcaloides vinca, imatinib (Gleevec), antraciclinas, rituximab, y trastuzumab.

26. Un uso de un compuesto de la reivindicación 18, para la preparación de un medicamento para el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM).

27. El uso de la reivindicación 26, en donde la condición es un cáncer seleccionado a partir de carcinoma de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon, melanoma, leucemia mieloide, mieloma múltiple, y eritroleucemia, adenoma de colon velloso, y osteosarcoma.

28. Un compuesto de las reivindicaciones 18 a 23, para utilizarse en el tratamiento de una condición mediante la modulación de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM).

29. El compuesto de la reivindicación 28, en donde la condición es un cáncer seleccionado a partir de carcinoma de

los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon, melanoma, leucemia mieloide, mieloma múltiple, y eritroleucemia, adenoma de colon velloso, y osteosarcoma.

30. Un compuesto de la fórmula II, seleccionado a partir del Cuadro I o del Cuadro II.

RESUMEN

Se proporcionan nuevos compuestos, composiciones y métodos de inhibición de la integración de la actividad del provirus de la cinasa Maloney (Cinasa PIM) asociada con tumorigénesis en un sujeto humano o animal. En ciertas modalidades, los compuestos y composiciones son efectivos para inhibir la actividad de cuando menos una cinasa PIM. Los nuevos compuestos y composiciones se pueden utilizar ya sea solos o bien en combinación con cuando menos un agente adicional para el tratamiento de un trastorno mediado por una cinasa de serina/treonina o por un receptor de cinasa de tirosina, tal como cáncer.

760

Ejemplo 99 (P.O.)

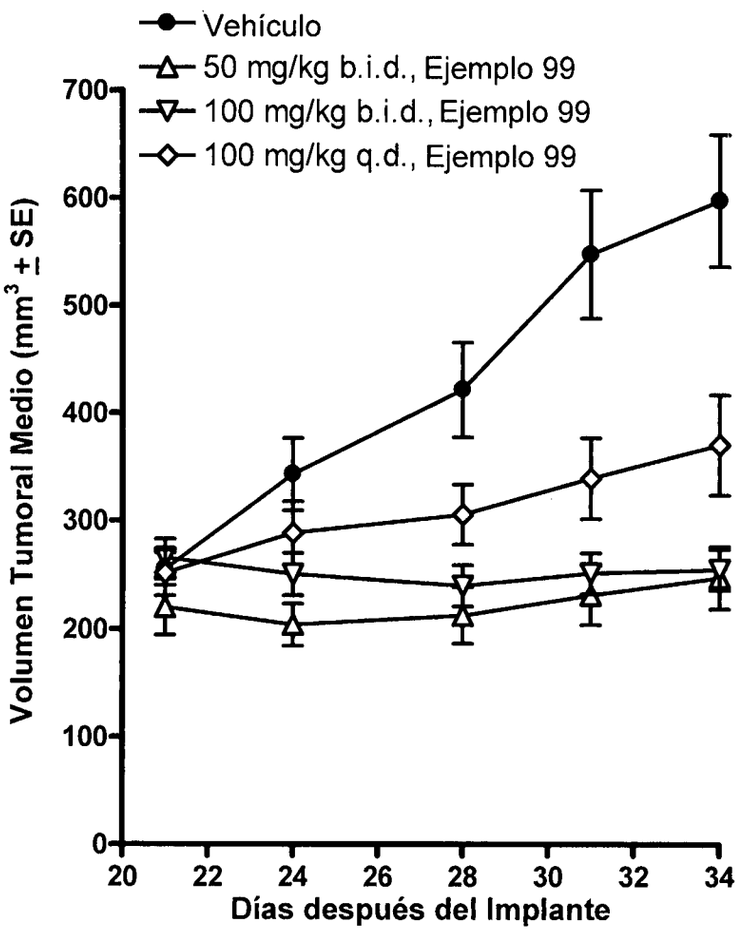


FIG. 1

Ejemplo 70 (P.O.)

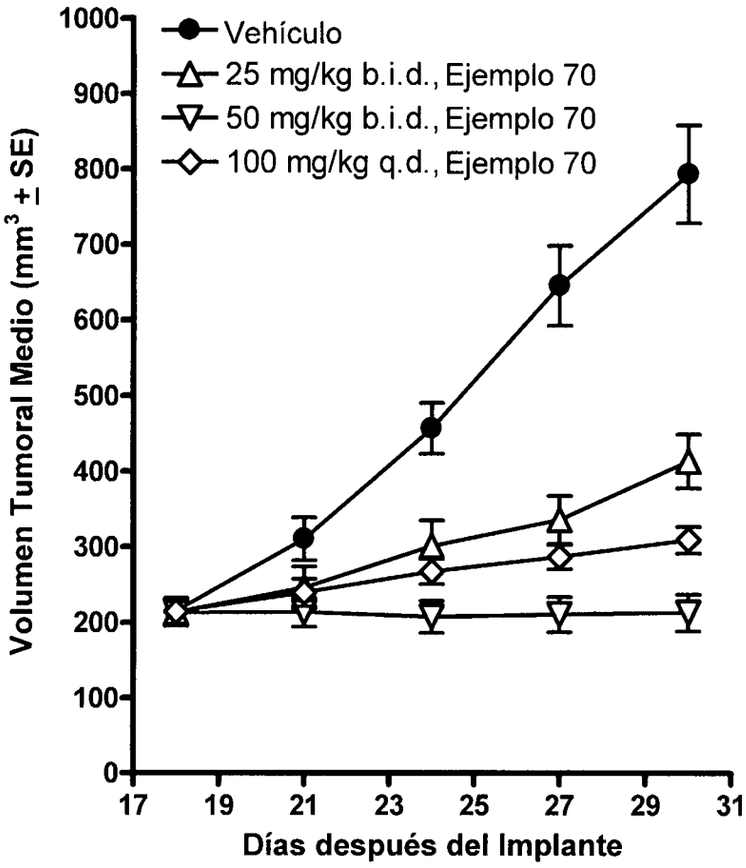


FIG. 2

Ejemplo 96 (P.O.)

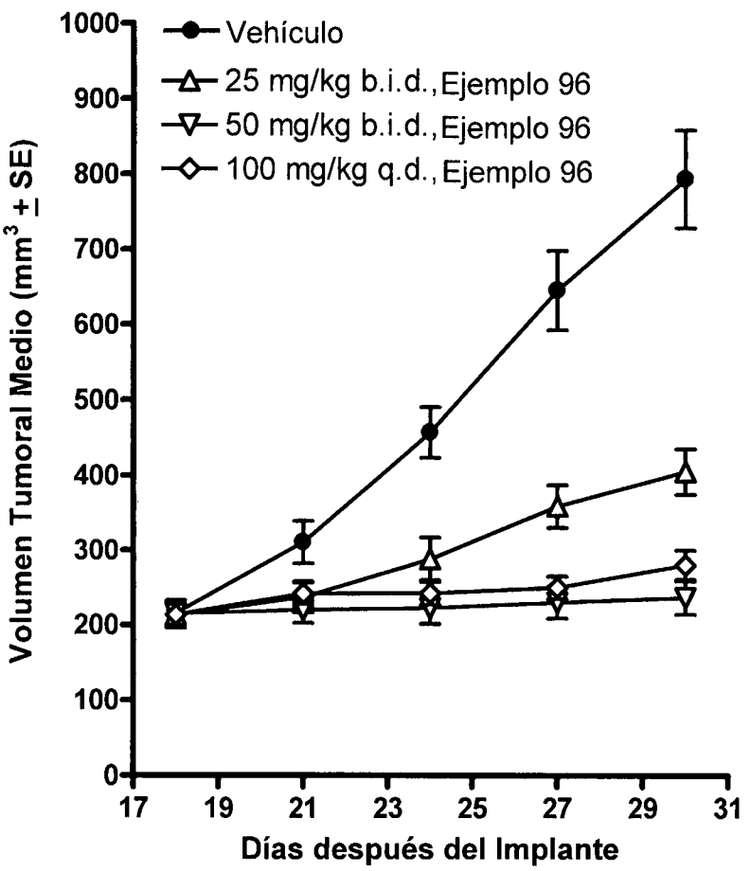


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/061205

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D401/14 A61K31/444 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2008/106692 A1 (NOVARTIS VACCINES & DIAGNOSTIC [US]; BURGER MATTHEW [US]; LINDVALL MIK) 4 September 2008 (2008-09-04) claims 1,7,13-23; examples 162,248,254,286,406,653; tables	1-28
X,P	WO 2009/014637 A2 (SCHERING CORP [US]; REDDY PANDURANGA ADULLA P [US]; ZHAO LIANYUN [US];) 29 January 2009 (2009-01-29) claims 1,184,185; example 244; tables	1-28
A	WO 01/55115 A1 (CYTOVIA INC [US]) 2 August 2001 (2001-08-02) page 8, line 22 - page 9, line 14; claims; example 3	1-28

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2009	18/11/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/061205

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/054702 A1 (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08) page 39, line 5 - page 41, line 5; claims page 6	1-28
A	WO 2008/054749 A1 (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08) page 197; claims; examples 173,171 page 6	1-28

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/061205

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008106692 A1	04-09-2008	AU 2008221263 A1	04-09-2008
		CA 2679659 A1	04-09-2008
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		AU 2007314342 A1	08-05-2008
		CA 2668210 A1	08-05-2008
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		CL 31382007 A1	27-06-2008
		EP 2078004 A1	15-07-2009

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-028419- -00000-0000
Fecha: 2011-03-08 16:24:30 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 264

PATENTE DE INVENCIÓN ☐ **MODELO**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

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- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
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- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐