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Organizacion y Digitalizacion CSA

PCT

Industria y Comercio

SUPERINTENDENCIA

10-110544

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: INHIBIDORES DE CINESA PIM Y MÉTODOS PARA SU USO

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 07 de Septiembr de 2010

P2010/000129

07-10-2010

OLARTERAISBECK
OLARTE RAISBECK MOURE &

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-110544- -00000-0000
Fecha: 2010-09-07 16:13:15 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 205

Industria y Comercio
SUPERINTENDENCIA

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000129**

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@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otr** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2009/052506 Fecha Marzo 3, 2009

Publicación Internacional No. WO 2009/109576 Fecha Septiembre 11, 2009

(6) **Título (54)** **INHIBIDORES DE CINASA PIM Y MÉTODOS PARA SU USO**

Clasificación Internacional (51) C07D 417/12, C07D 417/14, A61K 31/4439, A61P 35/00

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Marzo 3, 2008	61/033,359

(9) **Compr bante de pago No.** 10- **Fecha** Septiembre de 2010

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08 - 102832
- [x] Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la Regla 4.17(ii) PCT.
- [ ] 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.

3

LISTA DE INVENTORES

PCT/EP2009/052506

1. **Matthew BURGER,**
Novartis Vaccines and Diagnostics,
Inc., 4560 Horton Street, Emeryville,
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2. **Jiong LAN,**
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EstadoUnidos
Nacionalidad: China

3. **Mika LINDVALL**
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EstadoUnidos
Nacionalidad: Filandesa

4. **Gisele NISHIGUCHI,**
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Nacionalidad: Estadounidense

5. **Michelle TETALMAN,**
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EstadoUnidos
Nacionalidad: Estadounidense

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8001760

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-110544- -00000-0000

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Act. 411 PRESENTACION Folios: 205

RECIBO OFICIAL DE CAJA : 10 - 74,035
FECHA : SEPTIEMBRE 6 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754397	378391311	06/09/2010	3,379,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		554,000.00
		TOTAL :	$	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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 María 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 O
JORGE E. SIERR
Decreto 270 - 199

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 dia 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 Ofic
JORGE E. SERRA
Licencia 374 - 1993 P

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.

Teléfono: (57-1) 2182308, (57-1) 6232925.

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



Traductor Oficial
JORGE E. SIERRA
Licencia 376 - 1993

OLARTERAISBECK

OLARTE RAISBECK & FRIERI LTDA.

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

Zayda Chalela
Jacqueline Chapar
José Luis Londoño
Felipe Arredo
Simón Salin

Of Counsel
Guillermo Chalela
Gerardo Ric

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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 ends it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

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

Signature/Firma:

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Silvia Camonica

Pascal Marb

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 10, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

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)

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. 976 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)

This public document

2. is signed by .....

.....

3. acting in the capacity of .....

4. bears the seal/stamp of the .....

.....

Certified

5. At Basel-Baley

6. on .....

7. by the state Chancery of the Canton of Basel-Stadt

8. No .....

9. Seal/Stamp

10. Signature:

.....

Ueli Fischer

Sheet No. .....

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

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 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to the international application PCT/EP2009/052506,

Novartis AG, is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

Matthew BURGER, Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, CA 94608-2916, USA
Jiong LAN, Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, CA 94608-2916, USA
Mika LINDVALL, Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, CA 94608-2916, USA
Gisele NISHIGUCHI, Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, CA 94608-2916, USA
Michelle TETALMAN, Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, CA 94608-2916, USA

all dated March 17, 2009

to Novartis AG.

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 September 2009 (11.09.2009)

PCT

(10) International Publication Number
WO 2009/109576 A1

(51) International Patent Classification:
C07D 417/12 (2006.01) *A61K 31/4439* (2006.01)
C07D 417/14 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2009/052506

(22) International Filing Date:
3 March 2009 (03.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/033,359 3 March 2008 (03.03.2008) 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** [US/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). **LINDVALL, Mika** [FI/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). **TETALMAN, Michelle** [US/US]; Novartis Vaccines and Diagnostics, Inc., 4560 Horton Street, Emeryville, California 94608-2916 (US).

(74) Agent: VON SPRECHER, Georg; NOVARTIS PHARMA AG, Patent Department, 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, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

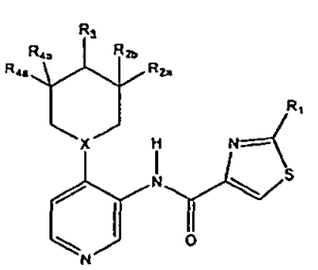
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

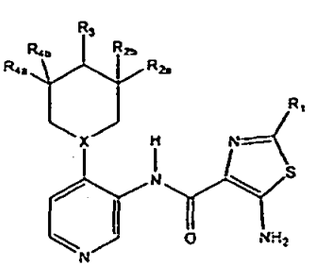
Published:

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

(54) Title: PIM KINASE INHIBITORS AND METHODS OF THEIR USE



(I)



(II)

(57) Abstract: The present invention relates to new compounds of Formulas (I) and (II), their tautomers, stereoisomers and polymorphs, 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 inhibition of Pim kinase activity and/or the prophylaxis or treatment of cancer.

WO 2009/109576 A1

PIM KINASE INHIBITORS AND METHODS OF THEIR USE

FIELD OF THE INVENTION

[0001] The present invention relates to new compounds, their tautomers, stereoisomers and polymorphs, 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

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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 maligmancies (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 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," *Biochim 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-

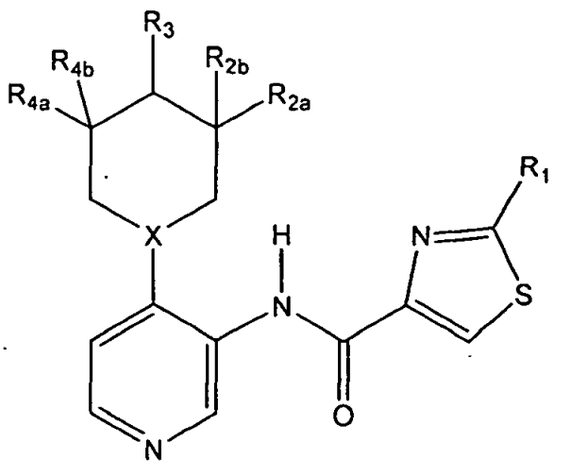
TAK1). A novel role for Pim-1 at the G2/M cell cycle checkpoint," *J Biol Chem* 179:48319-48328 (2004)) and NuMA (Bhattacharya N, et al., "Pim-1 associates with protein complexes necessary for mitosis, "*Chromosoma* 111(2):80-95 (2002)) and the protein synthesis regulator 4EBP1 (Hammerman PS et al, "Pim 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 THE INVENTION

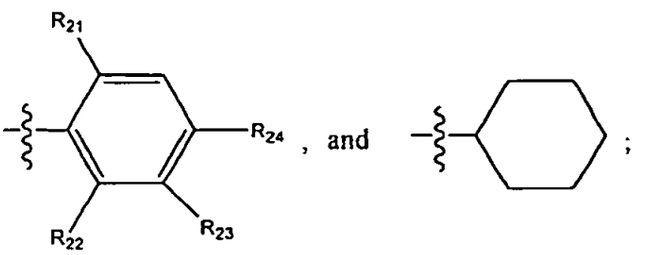
[0005] The present invention provides a compound of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



(I)

wherein,

R_1 is selected from



X represents CH, or N;

R_{2a} is selected from amino, methyl, CH_2F, CF_3, C_2H_5, and H;

R_{2b} is selected from H, and methyl;

R_3 is selected from H, OH, OCH_3, CH_3, F, and Cl;

R_{4a} is selected from amino, methyl, OH, OCH_3, OC_2H_5, F, CF_3, H, and ethyl;

R_{4b} is selected from methyl, H, and F;

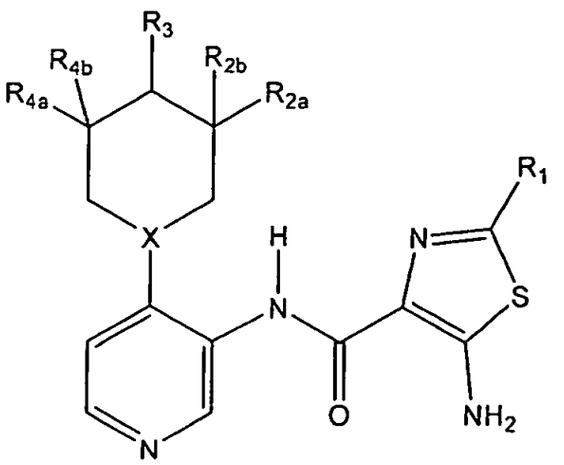
R_{21} represents H or F;

R_{22} represents H, Cl, or F;

R_{23} represents F, OC_2H_5, OCH_3, Cl, H, methyl, OH, or $OCH(CH_3)_2$; and

R_{24} represents H or OH.

[0006] In another aspect, the present invention provides a compound of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



II

wherein:

R_1 is selected from -NH-CO-alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

X represents CH or N;

R_{2a} is selected from -H, -OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo, amino and bezoate;

R_{2b} is selected from –H and alkyl;

R_3 is selected from H, OH, alkyl, alkoxy and halo;

R_{4a} is selected from –OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo and amino; and

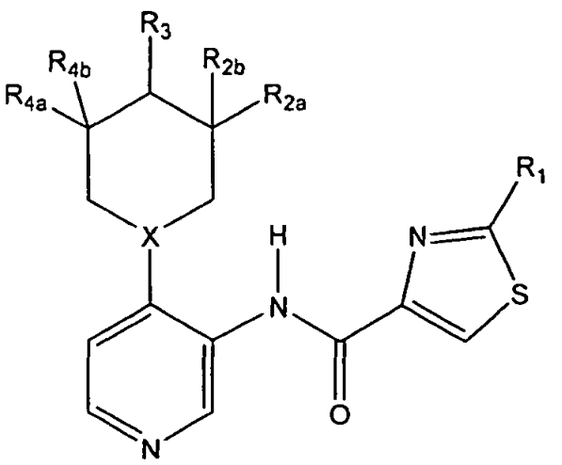
R_{4b} is selected from H, alkyl and halo.

[0007] Another aspect of the present invention provides a composition comprising a therapeutically effective amount of compound of Formula I or Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

[0008] Provided in another aspect of the present invention is a method for inhibiting PIM kinase activity in a cell, comprising contacting the cell with an effective amount of a compound of Formula I or Formula II. Yet another aspect 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 or Formula II.

DETAILED DESCRIPTION OF THE INVENTION

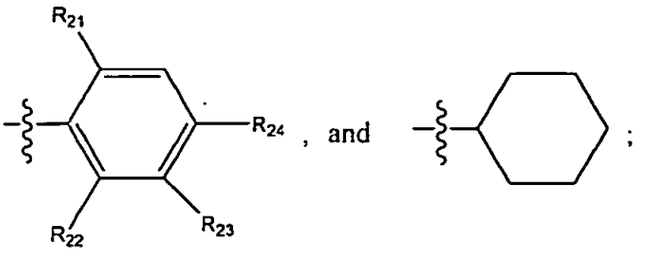
[0009] In one aspect, the present invention provides compounds of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



(I)

wherein,

R_1 is selected from



;

X represents CH, or N;

R_{2a} is selected from amino, methyl, CH_2F, CF_3, C_2H_5, and H;

R_{2b} is selected from H, and methyl;

R_3 is selected from H, OH, OCH_3, CH_3, F, and Cl;

R_{4a} is selected from amino, methyl, OH, OCH_3, OC_2H_5, F, CF_3, H, and ethyl;

R_{4b} is selected from methyl, H, and F;

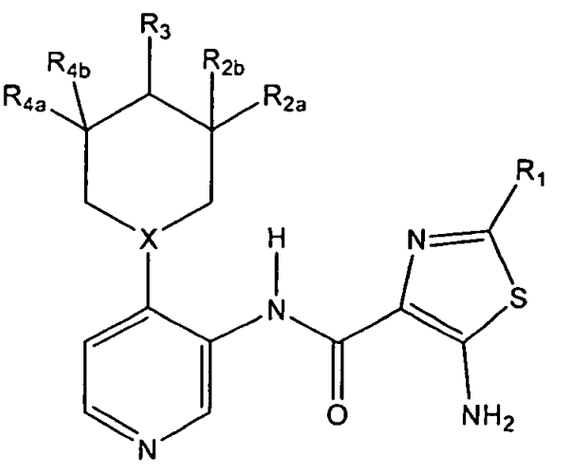
R_{21} represents H or F;

R_{22} represents H, Cl, or F;

R_{23} represents F, OC_2H_5, OCH_3, Cl, H, methyl, OH, or $OCH(CH_3)_2$; and

R_{24} represents H or OH.

[0010] In another aspect, the present invention provides a compound of Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



II

wherein:

R_1 is selected from -NH-CO-alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

X represents CH or N;

R_{2a} is selected from -H, -OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo, amino and bezoate;

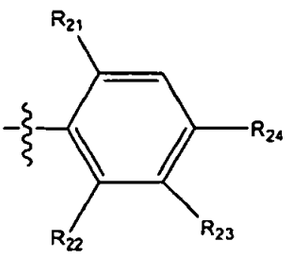
R_{2b} is selected from –H and alkyl;

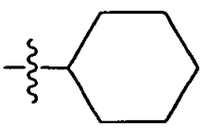
R_3 is selected from H, OH, alkyl, alkoxy and halo;

R_{4a} is selected from –OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo and amino; and

R_{4b} is selected from H, alkyl and halo.

[0011] In some aspects, the invention provides compounds of Formula II wherein R_1 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, and substituted or unsubstituted piperidinyl. In other aspects, the invention provides compounds of Formula II wherein R_1 is selected from



, and  ;

wherein:

R_{21} is H or halo;

R_{22} is H or halo;

R_{23} is selected from H, halo, alkyl and alkoxy; and

R_{24} is H or OH.

[0012] In some embodiments of the invention, R_{21} and R_{22} are independently selected from H or F. In other embodiments, R_{23} is selected from H, Cl, F, $-OC_2H_5$, $-OCH_3$, and $-OCH(CH_3)_2$.

[0013] In other embodiments, the invention provides compounds of formula II wherein R_2 is selected from H, methyl, ethyl, methoxy, ethoxy, fluoromethyl, trifluoromethyl, aminomethyl and hydroxymethyl.

[0014] Yet other embodiments provide compounds of formula II wherein R_3 is selected from H, -OH, methyl, methoxy, F and Cl.

[0015] In some embodiments, the invention provides compounds of formula II wherein R_{4a} is selected from -OH, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, amino, F and Cl. Other embodiments provide compounds of formula II wherein R_{4b} is selected from methyl and F.

[0016] In some presently preferred embodiments, the invention provides a compound of Formula I or Formula II selected from the group consisting of (S)-5-amino-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-ethylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-4-hydroxyphenyl)thiazole-4-carboxamide, 5-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-5-(fluoromethyl)piperidin-1-yl)-pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide, 5-amino-2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(3-ethoxy-2,6-difluorophenyl)-thiazole-4-carboxamide, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

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[0017] In other presently preferred embodiments, the invention provides a compound of Formula I or Formula II selected from the group consisting of (S)-5-amino-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-ethylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-4-hydroxyphenyl)thiazole-4-carboxamide, 5-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-5-(fluoromethyl)piperidin-1-yl)-pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide, 5-amino-2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0018] Another aspect of the present invention provides a composition comprising a therapeutically effective amount of compound of Formula I or Formula II, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

[0019] Provided in another aspect of the present invention is a method for inhibiting PIM kinase activity in a cell, comprising contacting the cell with an effective amount of a compound of Formula I or Formula II. Yet another aspect 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 or Formula II.

[0020] A preferred embodiment of this aspect of the present invention provides a method for treating a cancer disorder in a patient, comprising administering to the patient

a composition comprising an amount of a compound of Claim 1 or Claim 10 effective to inhibit PIM kinase activity in the patient

[0021] Other aspect of the present invention provides a compound of any Formula I or Formula II for use as a therapeutic agent. Yet another aspect of the present invention provides the use of any one of the compounds of Formula I or Formula II in the manufacture of a medicament for the treatment of cancer.

Definitions

[0022] "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 herein below.

[0023] 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.

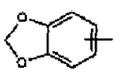
[0024] As used herein, the term "halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups. "Haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. The term "haloloweralkyl" refers to a lower alkyl radical substituted with one or more halogen atoms. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. The term "haloloweralkoxy" refers to a loweralkoxy radical substituted with one or more halogen atoms.

[0025] "Amino" refers herein to the group $-NH_2$, which may be substituted to form -NRR'. 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.

[0026] The term "alkoxy" refers to RO- wherein R is substituted or unsubstituted alkyl. Representative examples of loweralkoxy groups include methoxy, ethoxy, *t*-butoxy, trifluoromethoxy and the like.

[0027] "Cycloalkyl" refers to a mono- or polycyclic, heterocyclic or carbocyclic alkyl substituent. 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" or "heterocyclyl" 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.

[0028] "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.

[0029] "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, haloloweralkyl, loweralkylamino, haloloweralkylamino, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like.

[0030] 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.

[0031] 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.

[0032] It will also be apparent to those skilled in the art that the compounds of the invention, including the compounds of compounds of formulas (I) or (II) 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.

[0033] The compounds of the invention, including the compounds of formulas (I) or (II) 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.

[0034] As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of Formulas (I) or (II). These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formulas (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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] It will be apparent to those skilled in the art that the compounds of the invention, including the compounds of formulas (I) or (II) 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

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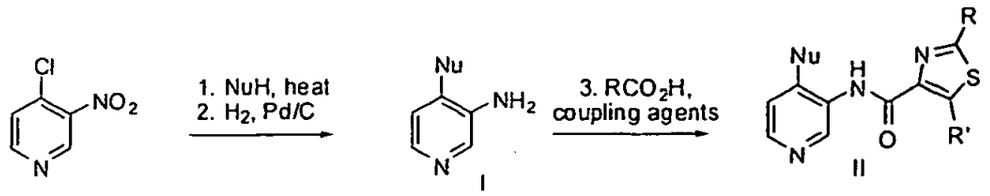
derivatives may be produced from the parent compound by various biochemical transformations in the subject such as, for example, oxidation, reduction, hydrolysis, or conjugation and include, for example, oxides and demethylated derivatives. The metabolites of a compound of the invention may be identified 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 formulas (I) or (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.

[0039] 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, mycloid disorders (e.g., myeloid leukemia, multiple myeloma and erythroleukemia), adenomas (e.g., villous colon adenoma) and sarcomas (e.g., osteosarcoma).

Synthetic Methods

[0040] The compounds of the invention can be obtained through procedures known to the skilled in the art. For example, as shown in Scheme 1, 4-chloro, 3-nitro pyridine can be reacted with a nucleophile yielding after nitro reduction a 4-substituted 3-amino pyridine I. The substituted amino pyridines I can be acylated with thiazolecarboxylic acids with the aid of coupling agents, or with acid halides or acid anhydrides yielding 3, 4 disubstituted pyridines II. If the 2 position R group of the thiazole is bromo, triflate or iodo, further modification to incorporate a variety of substituents at this position can be realized by metal mediated carbon-carbon bond forming reactions.

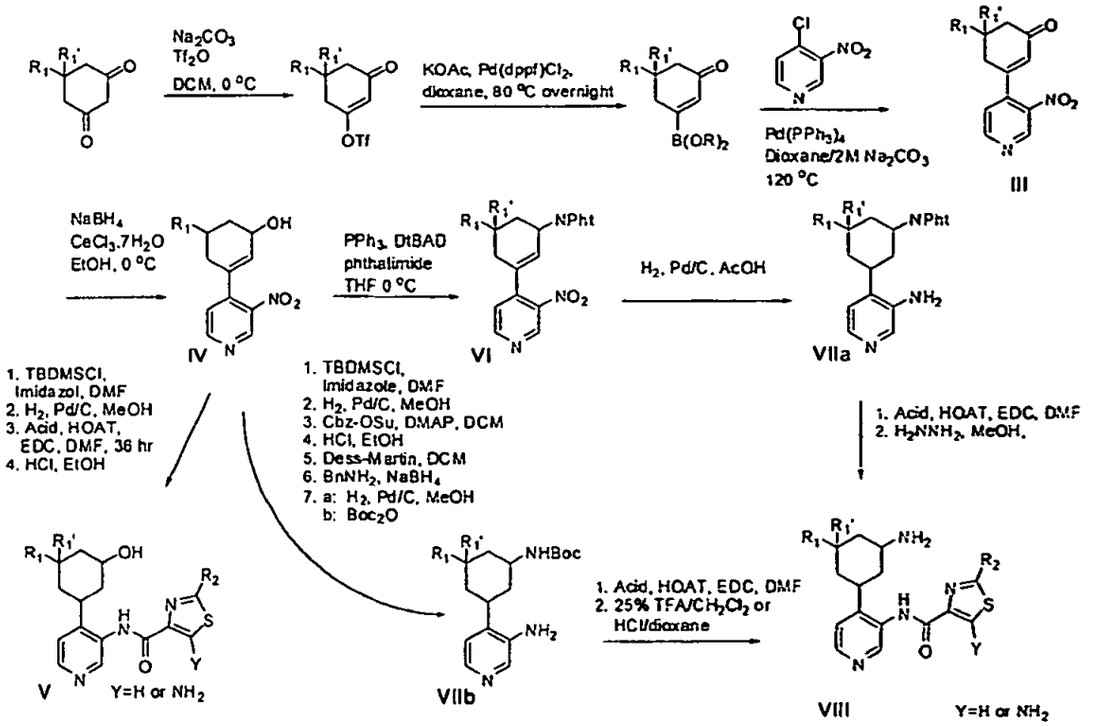
Scheme 1.



R'=H or NH2

[0041] The reaction of 4-chloro-3-nitropyridine with nucleophiles as depicted in Scheme 1 is not limited to nitrogen based nucleophiles; carbon-carbon bonds can be formed as well with the net addition of carbon nucleophiles. As shown in Scheme 2, cyclohexanediones can be converted via monotriflates to the corresponding cyclohexenoneboronate esters which can undergo palladium mediated carbon-carbon bond formation with 4-chloro, 3-nitro pyridine to yield nitropyridine substituted cyclohexenones III. Reduction of the enone functionality can yield a cyclohexenol IV which upon alcohol protection, nitro and alkene reduction, amide coupling and deprotection can yield cyclohexanol amides V. Cyclohexenol IV can also undergo Mitsunobo reaction with phthalimide to yield a protected aminocyclohexene V. Following nitro and alkene reduction, phthalimide protected aminocyclohexyl pyridyl aniline VIIa can undergo amide coupling and deprotection, to yield aminocyclohexane amides VIII. The corresponding Boc protected aminocyclohexane pyridyl aniline VIIb can also be prepared from cyclohexenol IV 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 benzyl deprotection and primary aliphatic amine Boc protection. In the amide products V and VIII, if R2 is halo or triflate, the amides IV and VIII can be further modified by standard modifications to introduce substituted aryls, alkyls and heteroaryls at R2. For example, if R2 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 R2 modifications are possible.

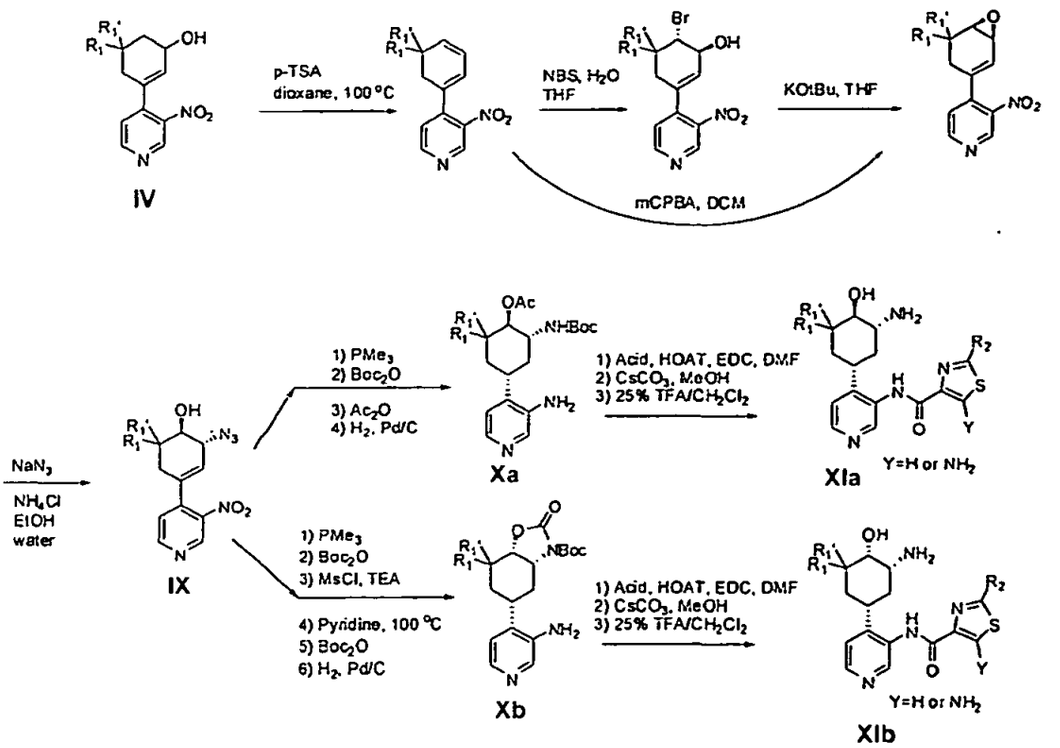
Scheme 2.



[0042] Thiazole amides with substituted cyclohexyl groups can be obtained by modification of nitropyridyl cyclohexenol IV. As shown in Scheme 3, cyclohexenol IV 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 IX. Cyclohexenyl azido alcohol IX can be converted to the trans protected amino hydroxy aniline Xa by azide reduction, alcohol protection and alkene and nitro reduction. Alternatively, the cyclohexenyl azido alcohol IX can be converted to the protected *cis* amino hydroxy aniline Xb 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 Xa and Xb can be converted to the corresponding thiazole amides XIa and XIb by amide coupling, acetate or cyclic carbamate cleavage and Boc deprotection. If R_2 is halo or triflate, the amides XIa and XIb and XII 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.

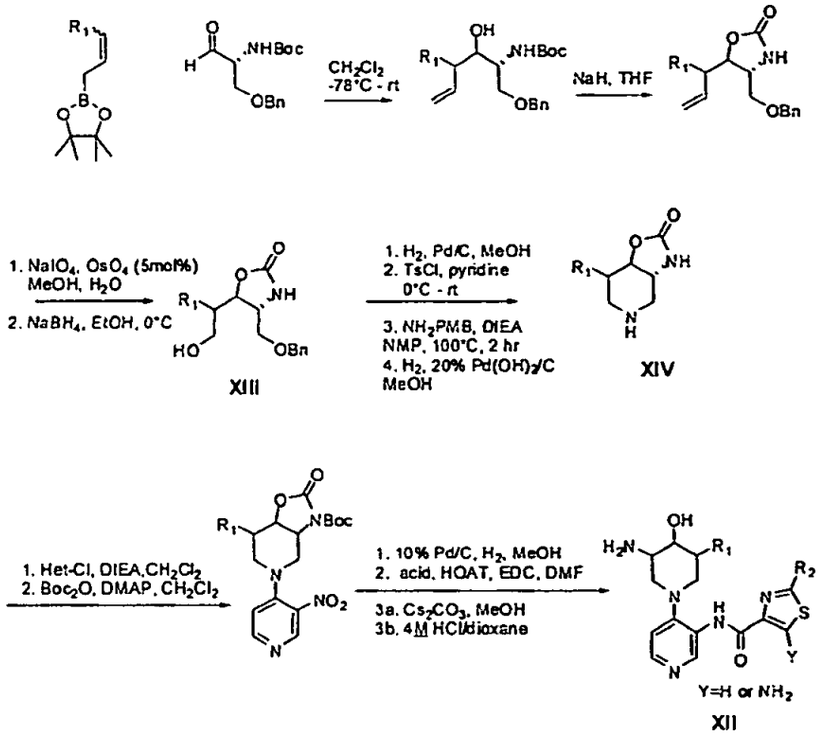
Scheme 3.



[0043] Substitued 3-aminopiperidines can be prepared and modified to yield substituted 3-aminopiperidinyl thiazole amides XII as depicted in Scheme 4.. Reaction of crotyl boronate esters with SerOBn aldehyde followed by cyclic carbamate formation, alkene oxidative cleavage and reduction yields hydroxyl compound XIII. Benzyl deprotection followed by bistosylation and reaction with p-methoxybenzylamine, and amine deprotection yields piperidine XIV. By use of chiral boronate esters, and different L and D serine derived aldehydes, all possible diastereomers of the resulting trisubstituted 5-alkyl, 4-hydroxy, 3-aminopiperidine can be obtained. Reaction of substituted piperidine XIV with 4-chloro-3-nitropyridine, followed by carbamate protection, nitro reduction, amide coupling, cyclic carbamate opening and deprotection yields

trisubstituted 5-methyl, 4-hydroxy, 3-aminopiperidinyl thiazole amides XII. If R_2 is halo or triflate, the amide XII 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 R2 modifications are possible.

Scheme 4.-



[0044] The compounds of the invention are useful *in vitro* 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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).

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] Representative side chains for use in the compounds of the following examples may generally be prepared in accordance with the following procedures:

EXAMPLES

[0061] 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.

[0062] 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).

[0063] 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.

[0064] 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.

[0065] GCMS analysis was performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 μL; initial column temperature: 50°C; final column temperature: 250°C; ramp time: 20 minutes; gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

[0066] Nuclear magnetic resonance (NMR) analysis can be performed with a Varian 300 or 400 MHz NMR (Palo Alto, CA). The spectral reference can either be TMS or the known chemical shift of the solvent.

[0067] The purity of some of the compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ).

[0068] Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

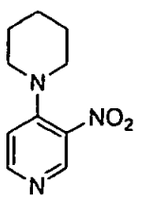
ABBREVIATIONS

Boc_2O	di-tert-butyl dicarbonate
DAST	(Diethylamino)sulfurtrifluoride
DCM	Dichloromethane
DIEA	diisopropylethylamine
DtBAD	Di-tert-butyl azodicarboxylate
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
MeCN	acetonitrile
MeOH	methanol
Na_2CO_3	sodium carbonate
$NaHCO_3$	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
TDMSCl	Tert-butyldimethylsilylchloride
TEA	triethylamine
THF	tetrahydrofuran
Tf2O	Triflic anhydride

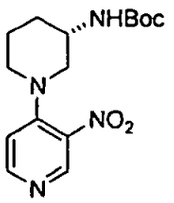
METHOD 1

Synthesis of 3-nitro-4-(piperidin-1-yl)pyridine



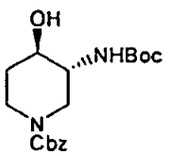
[0073] A solution of 4-chloro-3-nitropyridine (1.0 equiv.) and piperidine (2.0 equiv.) in ethanol, at a concentration of 0.5 M, was stirred at rt for 48 hours at which time the ethanol was removed *in vacuo*. The residue was partitioned between EtOAc (300 mL) and $Na_2CO_{3\,(sat.)}$ (75 mL), was washed further with H_2O (50 mL), $NaCl_{(sat.)}$ (50 mL), was dried over $MgSO_4$, was filtered and the volatiles were removed *in vacuo* yielding 3-nitro-4-(piperidin-1-yl)pyridine (95%). LCMS (*m/z*): 207.7 (MH^+); LC R_t = 1.60 min. ^1H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.31 (d, J=5.7, 1H), 6.84 (d, J=6.3, 1H), 3.18-3.21 (m, 4H), 1.64-1.78 (m, 6H).

Synthesis of (S)-tert-butyl 1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate

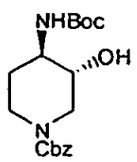


[0074] Method 1 was followed using 1 eq each of 4-chloro-3-nitropyidine, (S)-3-N-Boc-amino piperidine and diisopropylethylamine yielding (S)-tert-butyl 1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, (99 %). LCMS (*m/z*): 323.1 (MH^+); LC R_t = 2.13 min.

Synthesis of trans (+/-)-Benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate



Synthesis of trans (+/-)-Benzyl 4-(tert-butoxycarbonylamino)-3-hydroxypiperidine-1-carboxylate

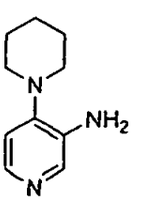


[0075] A solution of (+/-) benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (1.0 equiv.) in saturated ammonium hydroxide aqueous solution and ethanol (1:1, 0.05 M solution) in a sealed steel bomb was heated to 70 °C for 5 h. After all volatile materials were removed by N_2 gas stream, ethyl acetate and water were added for work-up. The crude regioisomeric mixture, benzyl 3-amino-4-hydroxypiperidine-1-carboxylate and benzyl 4-amino-3-hydroxypiperidine-1-carboxylate was reacted with Boc_2O (1.0 equiv.) and triethylamine (1.0 equiv.) in dichloromethane (0.1 M solution). After stirred for 2 h at room temperature, the reaction mixture was extracted with dichloromethane. The polar

(+/-)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate and nonpolar (+/-)-benzyl 4-(tert-butoxycarbonylamino)-3-hydroxypiperidine-1-carboxylate were obtained by flash column chromatography (20% to 40% EtOAc in hexanes, 28%, 51% each). LCMS (*m/z*): 351.1 (MH^+), R_t = 0.81 min, LCMS (*m/z*): 351.1 (MH^+), R_t = 0.83 min. The enantiomerically pure (3*S*,4*S*)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate and (3*R*,4*R*)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate were resolved by chiral HPLC (For analysis R_t = 6.8 min and 9.1 min respectively; n-heptane:ethanol= 70:30 (v:v), Chiralpak AD-H prep 250X4.6 mm at 1 mL/min. For preparative separation, n-heptane:ethanol = 80:20 (v:v), Chiralpak AS 50 x 500 mm.at 90 mL/min).

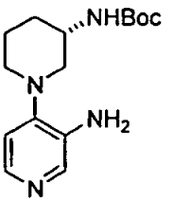
METHOD 2

Synthesis of 4-(piperidin-1-yl)pyridin-3-amine



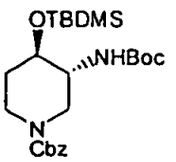
[0076] To a solution of 3-nitro-4-(piperidin-1-yl)pyridine (1.0 equiv.) in ethanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 15 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding 4-(piperidin-1-yl)pyridin-3-amine (93%) as an oil. LCMS (*m/z*): 178.0 (MH^+); LC R_t = 1.68 min. ^1H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.96 (d, J=5.4, 1H), 6.78 (d, J=5.1, 1H), 3.64-3.74 (m, 2H), 2.86-2.94 (m, 4H), 1.66-1.78 (m, 4H), 1.58-1.64 (m, 2H).

Synthesis of (S)-tert-butyl 1-(3-aminopyridin-4-yl)piperidin-3-ylcarbamate



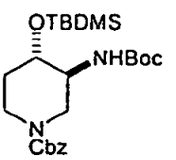
[0077] Following Method 2, (S)-tert-butyl 1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced yielding (S)-tert-butyl 1-(3-aminopyridin-4-yl)piperidin-3-ylcarbamate, (78%). LCMS (*m/z*): 293.1 (MH^+); LC R_t = 2.08 min.

Synthesis of (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate



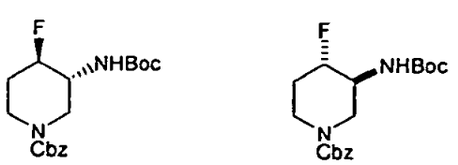
[0078] To a solution of (3*R*,4*R*)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate (1.0 equiv.) in dichloromethane (0.1 M solution) was added imidazole (1.1 equiv.), DMAP (0.1 equiv.), and TBDMSCl (1.1 equiv.) sequentially. The reaction mixture was stirred at room temperature for 20 h. After worked up with dichloromethane, the crude material was purified by silica column chromatography (10% to 20% EtOAc in hexanes) yielding (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate (76%). LCMS (*m/z*): 365.2 [(M-Boc)H^+]; LC R_t = 6.05 min.

Synthesis of (3S, 4S)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate



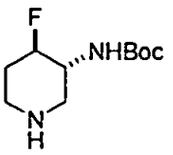
[0079] To a solution of (3*S*,S*R*)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate (1.0 equiv.) in dichloromethane (0.1 M solution) was added imidazole (1.1 equiv.), DMAP (0.1 equiv.), and TBDMSCl (1.1 equiv.) sequentially The reaction mixture was stirred at room temperature for 20 h. After worked up with dichloromethane, the crude material was purified by silica column chromatography (10% to 20% EtOAc in hexanes) yielding (3S,4S)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate. LCMS (*m/z*): 365.2 [(M-Boc)H^+]; LC R_t = 6.05 min.

Synthesis of (3*R*,4*R*)-Benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate and (3*S*,4*S*)-Benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate



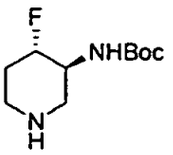
[0080] To a solution of (+/-)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate (1.0 equiv.) in dichloromethane (0.3 M solution) was added DAST at -78 °C. The reaction mixture was slowly warmed up to room temperature for 15 h. After quenched with saturated sodium bicarbonate aqueous solution, ethyl acetate and water were added for work-up. The (+/-)-benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate was obtained by silica column chromatography (30% EtOAc in hexanes, 40%). LCMS (*m/z*): 253.1[(M-Boc)H^+];; LC R_t = 4.08 min. The enantiomerically pure (3*R*,4*R*)-benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate and (3*S*,4*S*)-benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate were resolved by chiral HPLC (for analysis: R_t = 9.4 min and 12.6 min respectively; n-heptane:isopropanol = 90:10 (v:v), Chiralpak AS 250 x 4.6 mm at 1 mL/min. For preparative separation, n-heptane:isopropanol = 90:10 (v:v), Chiralpak AS 50 x 500 mm.at 90 mL/min).

Synthesis of tert-butyl (3R,4R)-4-fluoropiperidin-3-ylcarbamate



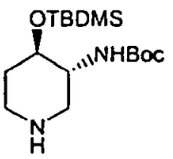
[0081] Method 2 was followed using (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate (1.0 equiv.) yielding crude tert-butyl (3R,4R)-4-fluoropiperidin-3-ylcarbamate, (93%). LCMS (*m/z*): 219.2 (MH^+), LC R_t = 0.45 min.

Synthesis of tert-butyl (3S,4S)-4-fluoropiperidin-3-ylcarbamate



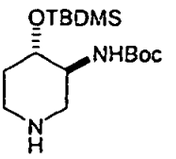
[0082] Method 2 was followed using (3S,4S)-benzyl 3-(tert-butoxycarbonylamino)-4-fluoropiperidine-1-carboxylate (1.0 equiv.) yielding crude (+/-)-tert-butyl 4-fluoropiperidin-3-ylcarbamate, (93%). LCMS (*m/z*): 219.2 (MH^+), LC R_t = 0.45 min.

Synthesis of tert-butyl (3R,4R)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate



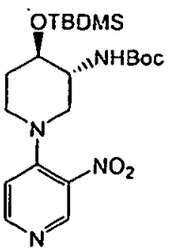
[0083] Method 2 was followed using (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate (1.0 equiv.) yielding crude tert-butyl (3R,4R)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 331.3 (MH^+).

Synthesis of tert-butyl (3R,4R)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate



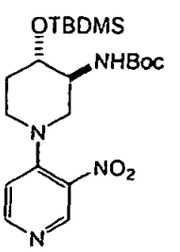
[0084] Method 2 was followed using (3S,4S)-benzyl 3-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate (1.0 equiv.) yielding crude tert-butyl (3S,4S)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 331.3 (MH^+).

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



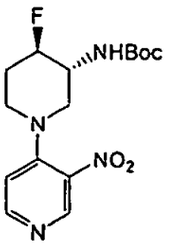
[0085] Method 1 was followed using 1 eq each of 4-chloro-3-nitropyridine, tert-butyl (3R,4R)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate and triethylamine in DMF yielding tert-butyl (3R,4R)-4-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, (98%). LCMS (*m/z*): 453.3 (MH^+); LC R_t = 4.01 min.

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



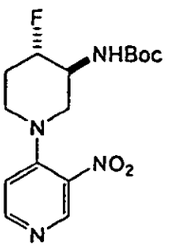
[0086] Method 1 was followed using 1 eq each of 4-chloro-3-nitropyridine, tert-butyl (3S,4S)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate and triethylamine in DMF yielding tert-butyl (3S,4S)-4-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, (98%). LCMS (*m/z*): 453.3 (MH^+); LC R_t = 4.01 min.

Synthesis of tert-butyl (3R,4R)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



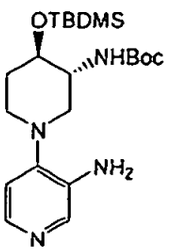
[0087] Method 1 of Example 1 was followed using 1 eq each of 4-chloro-3-nitropyridine, tert-butyl (3R,4R)- 4-fluoropiperidin-3-ylcarbamate and triethylamine in ethanol yielding tert-butyl (3R,4R)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, (91%). LCMS (*m/z*): 341.0 (MH^+); LC R_t = 2.37 min.

Synthesis of tert-butyl (3S,4S)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



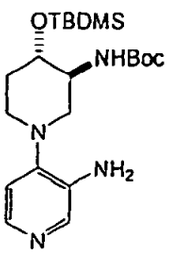
[0088] Method 1 of Example 1 was followed using 1 eq each of 4-chloro-3-nitropyridine, tert-butyl (3S,4S)- 4-fluoropiperidin-3-ylcarbamate and triethylamine in ethanol yielding tert-butyl (3S,4S)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, (91%). LCMS (*m/z*): 341.0 (MH^+); LC R_t = 2.37 min.

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



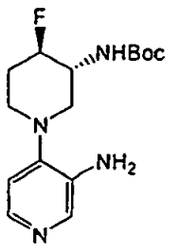
[0089] Following method 2, tert-butyl (3R,4R)- 4-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate in ethanol and ethyl acetate (1:1, 0.1 M solution) was reduced yielding tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 423.2 (MH^+); LC R_t = 3.78 min.

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



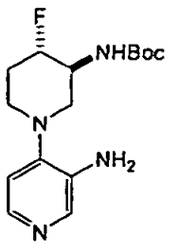
[0090] Following method 2, tert-butyl (3R,4R)- 4-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate in ethanol and ethyl acetate (1:1, 0.1 M solution) was reduced yielding tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 423.2 (MH^+); LC R_t = 3.78 min.

Synthesis of tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-fluoropiperidin-3-ylcarbamate



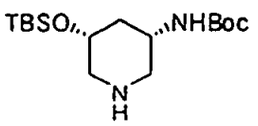
[0091] Following method 2, tert-butyl (3R,4R)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate in ethanol and ethyl acetate (1:1, 0.1 M solution) was reduced yielding tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-fluoropiperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 311.2 (MH^+); LC R_t = 2.14 min.

Synthesis of tert-butyl (3S,4S)-1-(3-aminopyridin-4-yl)-4-fluoropiperidin-3-ylcarbamate



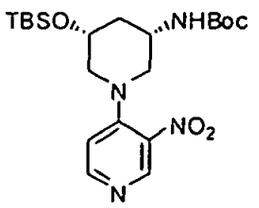
[0092] Following method 2, tert-butyl (3S,4S)-4-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate in ethanol and ethyl acetate (1:1, 0.1 M solution) was reduced yielding tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-fluoropiperidin-3-ylcarbamate, (>99%). LCMS (*m/z*): 311.2 (MH^+); LC R_t = 2.14 min.

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



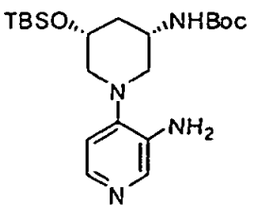
[0093] tert-Butyl (3S,5R)-5-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate was prepared according to the patent procedure as described by Y, Zhou; WO2005028467.

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



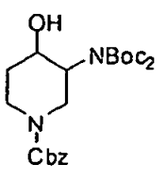
[0094] Method 1 was followed was followed using tert-Butyl (3S,5R)-5-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, yielding tert-butyl (3S,5R)-5-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate. LC/MS (*m/z*): 453.2 (MH^+).

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



[0095] Method 2 was followed using tert-butyl (3S,5R)-5-(tert-butyldimethylsilyloxy)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate, yielding tert-butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate. LC/MS (*m/z*): 423.2 (MH^+).

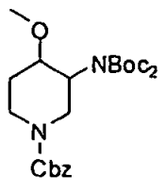
Synthesis of trans (+/-)-benzyl 3-(bis(tert-butoxycarbonyl)amino)-4-hydroxypiperidine-1-carboxylate



[0096] To a solution of trans (+/-)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate (1.0 equiv.) in DCM and CH_3CN (1:1, 0.14 M) was

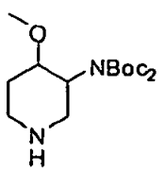
added BOC_2O (1.0 equiv.), triethylamine (1.5 equiv.), and DMAP (catalytic amount). The reaction was stirred at room temperature for 15 h, upon which time the solution was concentrated and purified via silica gel column chromatography eluting with EtOAc and hexanes (1:6) to give the desired product as a white foam. LCMS (*m/z*): 451.1 (MH^+).

Synthesis of trans (+/-)-benzyl 3-(bis(tert-butoxycarbonyl)amino)-4-methoxypiperidine-1-carboxylate



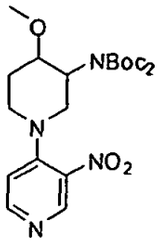
[0097] To a solution of NaH (1.3 equiv.) in THF (0.1M) was added benzyl 3-(bis(tert-butoxycarbonyl)amino)-4-hydroxypiperidine-1-carboxylate (1.0 equiv.) and the reaction was heated to 50 °C for 10 min. Upon cooling to room temperature, MeI (1.5 equiv.) was added and the solution was allowed to stir for 16 h. The reaction was quenched with water, then extracted with EtOAc, the organic was dried with brine and Na_2SO_4, and concentrated. The crude material was purified via silica gel column chromatography eluting with EtOAc and hexanes (1:3) to give a clear oil in 71% yield. LCMS (*m/z*): 365.0 (MH^+).

Synthesis of trans (+/-)-3-(bis(tert-butoxycarbonyl)amino)-4-methoxypiperidine



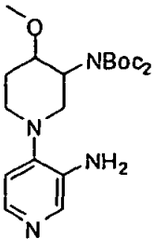
[0098] Method 2 was followed using trans (+/-)-benzyl 3-(bis(tert-butoxycarbonyl)amino)-4-methoxypiperidine-1-carboxylate (1.0 equiv.) yielding crude trans (+/-)-3-(bis(tert-butoxycarbonyl)amino)-4-methoxypiperidine that was used for the next step without further purification. LCMS (*m/z*):331.2 (MH^+)

Synthesis of trans (+/-)-N,N-di-BOC-4-methoxy-1-(3-nitropyridin-4-yl)piperidin-3-amine



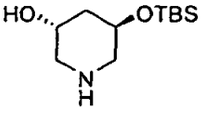
[0099] Method 1 was followed using trans (+/-)-3-(bis(tert-butoxycarbonyl)amino)-4-methoxypiperidine (1.0 equiv.), 4-chloro-3-nitropyridine (1.2 equiv.), and DIEA (4.0 equiv.) to give trans (+/-)-N,N-di-BOC-4-methoxy-1-(3-nitropyridin-4-yl)-piperidin-3-amine after column chromatography (EtOAc and hexanes, 50%) in 59% yield for two steps. LCMS (*m/z*): 453.2 (MH^+), LC R_t = 3.24 min.

Synthesis of trans (+/-)-N,N-di-BOC-4-methoxy-1-(3-aminopyridin-4-yl)piperidin-3-amine



[0100] Method 2 was followed using trans (+/-)-N,N-di-BOC-4-methoxy-1-(3-nitropyridin-4-yl)-piperidin-3-amine to give trans (+/-)-N,N-di-BOC-4-methoxy-1-(3-aminopyridin-4-yl)piperidin-3-amine in >95% yield as a clear oil. LCMS (*m/z*): 423.0 (MH^+), LC R_t = 3.10 min.

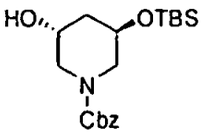
Synthesis of of (3R,5R)-5-(tert-butyldimethylsilyloxy)piperidin-3-ol



[0101] (3R,5R)-5-(tert-butyldimethylsilyloxy)piperidin-3-ol was prepared according to the patent procedure as described by Zhou, Y. WO2005028467.

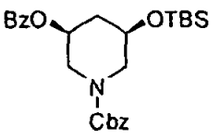
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Synthesis of (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypiperidine-1-carboxylate



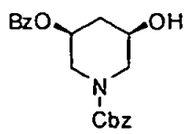
[0102] To a solution of (3R,5R)-5-(tert-butyldimethylsilyloxy)piperidin-3-ol (1 eq) in 20 mL of 1,4-dioxane and 8 mL of water was added benzyl chloroformate (1.5 eq). The mixture was stirred at room temperature for 4 hours. The crude mixture was diluted with 100 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 3) to yield (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypiperidine-1-carboxylate (74%). LC/MS (*m/z*): 366.2 (MH^+).

Synthesis of (3S,5R)-benzyl 3-(benzoyloxy)-5-(tert-butyl-dimethylsilyloxy)piperidine-1-carboxylate



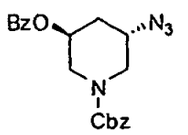
[0103] To a stirring 0°C solution of triphenylphosphine (1.2 equiv) in 23 mL of THF was added di-tert-butyl azodicarboxylate (1.2 equiv). The mixture was stirred at 0°C for 10 minutes. Then a solution of (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypiperidien-1-carboxylate (1.0 equiv) in 11 mL of THF was added and stirred for 20 minutes at 0°C. Benzoic acid (1.2 equiv) was then added and the reaction mixture was allowed to slowly warm to rt. After 16 hours the reaction mixture was concentrated *in vacuo* then diluted with EtOAc and washed with water then brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes = 1 : 8) to yield (3S,5R)-benzyl 3-(benzoyloxy)-5-(tert-butyl-dimethylsilyloxy)piperidine-1-carboxylate (77%). LC/MS (*m/z*): 470.2 (MH^+), HPLC R_t = 6.05min.

Synthesis of (3S,5R)-benzyl 3-(benzoyloxy)-5-hydroxypiperidine-1-carboxylate



[0104] To a solution of (3S,5R)-benzyl 3-(benzoyloxy)-5-(tert-butyl-dimethylsilyloxy)-piperidine-1-carboxylate (1 eq) in 30 mL of methanol was added 3.8M HCl in isopropanol (4 eq). The reaction mixture was allowed to stand at room temperature for 3 hours at which point it was concentrated under reduced pressure. The resulting residue was diluted with 120 mL of EtOAc, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to yield (3S,5R)-benzyl 3-(benzoyloxy)-5-hydroxypiperidine-1-carboxylate (95%). LC/MS (*m/z*): 355.9 (MH^+). HPLC: R_t: 3.62 min.

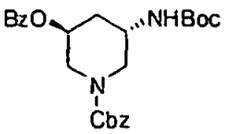
Synthesis of (3S,5S)-benzyl 3-azido-5-(benzoyloxy)piperidine-1-carboxylate



[0105] To a solution of (3S,5R)-benzyl 3-(benzoyloxy)-5-hydroxypiperidine-1-carboxylate (1 eq) in 20 mL of dichloromethane was added triethyl amine (3 eq) and methanesulfonyl chloride (1.5 eq) at 0°C. The reaction mixture was allowed to stir at room temperature for 2 hours. The crude mixture was diluted with 120 mL of EtOAc, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was dissolved in 25 mL of NMP. Sodium azide (2.2eq) was added and the resulting suspension was stirred at 80°C overnight. The reaction mixture was diluted with 200 mL of EtOAc and 100 mL of hexanes, washed with water, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 2) to yield (3S,5S)-benzyl 3-azido-5-(benzoyloxy)piperidine-1-carboxylate (88%). LC/MS (*m/z*): 381.0 (MH^+). HPLC: R_t: 4.41 min.

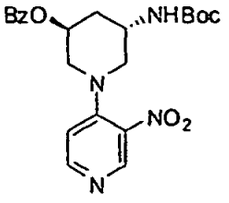
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Synthesis of (3S,5S)-benzyl 3-(benzoyloxy)-5-(tert-butoxycarbonylamino)-piperidine-1-carboxylate



[0106] To a solution of (3S,5S)-benzyl 3-azido-5-(benzoyloxy)piperidine-1-carboxylate (1 eq) in a mixture of 14 mL of pyridine and 2 mL of ammonium hydroxide was added 1M trimethylphosphine (3 eq) at room temperature. The reaction mixture was stirred at room temperature for 3 hours at which point the solvents were removed under reduced pressure to give a yellow oil. The oil was again dissolved in 100 mL of ethanol and concentrated to remove ammonium hydroxide completely. The residue was dissolved in 24 ml of 1,4-dioxane and 24 mL of sat. aq. $NaHCO_3$ was added. Di-tert-butyl dicarbonate (4 eq) in 12 mL of THF was added dropwise at 0°C. The mixture was allowed to stir at room temperature for 2 hours. The crude mixture was diluted with 200 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 2) to yield (3S,5S)-benzyl 3-(benzoyloxy)-5-(tert-butoxycarbonylamino)-piperidine-1-carboxylate (92%). LC/MS (*m/z*): 455.1 (MH^+). HPLC: R_t: 4.38 min.

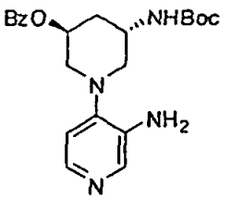
Synthesis of (3S,5S)-5-(tert-butoxycarbonylamino)-1-(3-nitropyridin-4-yl)-piperidin-3-yl benzoate



[0107] To a solution of (3S,5S)-benzyl 3-(benzoyloxy)-5-(tert-butoxycarbonylamino)-piperidine-1-carboxylate (1 eq) in 15 methanol and 15 mL of EtOAc was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere for 4 hours. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo*. The residue was

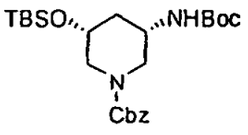
dissolved in 20 mL of isopropanol and DIPEA (1.8 eq) and 4-chloro-3-nitropyridine (1.2 eq) were added. The reaction mixture was stirred at 75°C for 2 hours, at which point the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 150 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to yield (3S,5S)-5-(tert-butoxycarbonylamino)-1-(3-nitropyridin-4-yl)-piperidin-3-yl benzoate (90%). LC/MS (*m/z*): 443.2 (MH^+). HPLC: R_t: 2.89 min.

Synthesis of (3S,5S)-1-(3-aminopyridin-4-yl)-5-(tert-butoxycarbonylamino)piperidin-3-yl benzoate



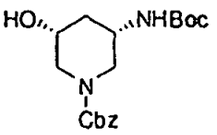
[0108] Following Method 2, (3S,5S)-5-(tert-butoxycarbonylamino)-1-(3-nitropyridin-4-yl)-piperidin-3-yl benzoate was reduced to yield (3S,5S)-1-(3-aminopyridin-4-yl)-5-(tert-butoxycarbonylamino)piperidin-3-yl benzoate. LC/MS (*m/z*): 413.1 (MH^+). HPLC: R_t: 2.75 min.

Synthesis of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate



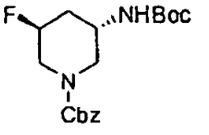
[0109] Followed method to synthesis of (3S,5S)-benzyl 3-(benzoyloxy)-5-(tert-butoxycarbonylamino)-piperidine-1-carboxylate starting from (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypiperidine-1-carboxylate. LC/MS (*m/z*): 365.2 (MH^+-Boc), Rt: 1.37.

Synthesis of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-hydroxypiperidine-1-carboxylate



[0110] To a solution of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-(tert-butyldimethylsilyloxy)piperidine-1-carboxylate (1eq) in 30 mL of THF was added 5.2 mL of TBAF (1.2eq). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5% methanol in EtOAc : hexanes= 1 : 1) to yield (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-hydroxypiperidine-1-carboxylate (100%). LC/MS (*m/z*): 251.2 (MH^+), Rt: 0.89. HPLC: R_t: 3.26 min.

Synthesis of (3S,5S)-benzyl 3-(tert-butoxycarbonylamino)-5-fluoropiperidine-1-carboxylate



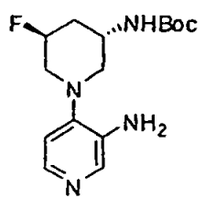
[0111] To a solution of the (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-hydroxypiperidine-1-carboxylate (1 eq) in 5 mL of dichloromethane was added DAST (1.35 eq). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with 120 mL of ethyl acetate, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 3) to yield tert-butyl (3S,5S)-1-(3-aminopyridin-4-yl)-5-fluoropiperidin-3-ylcarbamate (30%). LC/MS (*m/z*): 253.1 (MH^+-100), R_t = 0.96 min. HPLC: R_t: 3.79 min.

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



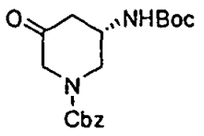
[0112] To a solution of (3S,5S)-benzyl 3-(tert-butoxycarbonylamino)-5-fluoropiperidine-1-carboxylate (1 eq) in 5 methanol and 5 mL of EtOAc was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere for 4 hours. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo*. The residue was dissolved in 5 mL of isopropanol and DIPEA (1.8 eq) and 4-chloro-3-nitropyridine (1.5 eq) were added. The reaction mixture was stirred at 65°C for 3 hours, at which point the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 120 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to give tert-butyl (3S,5S)-5-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (78%). LC/MS (*m/z*): 341.1 (MH^+), R_t = 0.57 min. HPLC: R_t: 2.01 min.

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



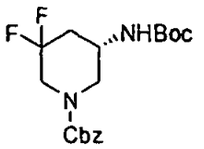
[0113] Following Method 2, tert-butyl (3S,5S)-5-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced to yield tert-butyl (3S,5S)-1-(3-aminopyridin-4-yl)-5-fluoropiperidin-3-ylcarbamate.. LC/MS (*m/z*): 311.1 (MH^+), R_t = 0.54 min. HPLC: R_t: 1.76 min.

Synthesis of (S)-benzyl 3-(tert-butoxycarbonylamino)-5-oxopiperidine-1-carboxylate



[0114] To a solution of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-hydroxypiperidine-1-carboxylate (1eq) in 10 mL dichloromethane was added Dess-Martin periodinane (1.2 eq) at room temperature. The reaction mixture was stirred at that temperature overnight. The mixture was diluted with ethyl acetate, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 2) to yield (S)-benzyl 3-(tert-butoxycarbonylamino)-5-oxopiperidine-1-carboxylate (81%). LC/MS (*m/z*): 249.1 (MH^+-100), R_t: 0.83 min. HPLC: R_t: 3.26 min.

Synthesis of 5-(tert-butoxycarbonylamino)-3,3-difluoropiperidine-1-carboxylate



[0115] To a solution of the (S)-benzyl 3-(tert-butoxycarbonylamino)-5-oxopiperidine-1-carboxylate (1 eq) in 25 mL of dichloromethane was added DAST (20eq). The reaction mixture was stirred at room temperature 3 hours. The reaction was quenched by *aq.* sodium bicarbonate. The resulting mixture was extracted with ethyl acetate. The organic layer was separated and washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 2) to yield 5-(tert-butoxycarbonylamino)-3,3-difluoropiperidine-1-carboxylate (52%). LC/MS (*m/z*): 271.1 (-Boc), R_t: 0.99min.

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



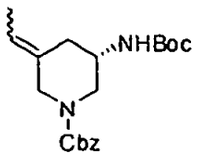
[0116] To a solution of 5-(tert-butoxycarbonylamino)-3,3-difluoropiperidine-1-carboxylate (1 eq) in 5 mL of methanol and 5 mL of EtOAc was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere overnight. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo*. The residue was dissolved in 5 mL of isopropanol and DIPEA (2.0 eq) and 4-chloro-3-nitropyridine (1.5 eq) were added. The reaction mixture was stirred at 70°C for 3 hours, at which point the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 120 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5 % methanol in EtOAc : hexanes= 1 : 1) to yield (S)-tert-butyl 5,5-difluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (19%). LC/MS (*m/z*): 359.0 (MH^+), R_t: 0.65 min.

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



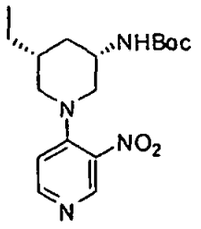
[0117] Following Method 2, (S)-tert-butyl 5,5-difluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced to yield (S)-tert-butyl 1-(3-aminopyridin-4-yl)-5,5-difluoropiperidin-3-ylcarbamate. LC/MS (*m/z*): 329.0 (MH^+), R_t: 0.62 min.

Synthesis of (S)-benzyl 3-(tert-butoxycarbonylamino)-5-ethylidenepiperidine-1-carboxylate



[0118] To a suspension of ethyltriphenylphosphonium bromide (11eq) in 14 mL of THF was added potassium tert-butoxide (10eq) at room temperature. The reaction mixture was stirred at that temperature for 20 minutes. Then the reaction was cooled to 0°C, and (S)-benzyl 3-(tert-butoxycarbonylamino)-5-oxopiperidine-1-carboxylate (1eq) in 7 mL of THF was added to the reaction mixture. The reaction was allowed to warm up room temperature. After being stirred for 40 minutes, the reaction mixture was poured into *aq.* sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated and washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was purified by flash chromatography (EtOAc : hexanes= 2 : 1) to yield (S)-benzyl 3-(tert-butoxycarbonylamino)-5-ethylidenepiperidine-1-carboxylate. LC/MS (*m/z*): 261.2 (MH^+-100), R_t: 1.12 min. HPLC: R_t: 4.31 min.

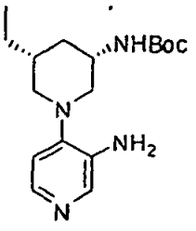
Synthesis of tert-butyl (3S,5R)-5-ethyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



[0119] To a solution of (S)-benzyl 3-(tert-butoxycarbonylamino)-5-ethylidenepiperidine-1-carboxylate (1 eq) in 5.5 mL of ethanol and 5.5 mL of EtOAc was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere for 45 minutes. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo.* The residue was dissolved in 1.4 mL of isopropanol and DIPEA (2.5 eq) and 4-chloro-3-nitropyridine (1.5 eq) were added. The reaction mixture was stirred at 80°C overnight, at which point the reaction mixture

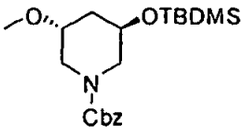
was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 120 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to yield tert-butyl (3S,5R)-5-ethyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (91%). LC/MS (*m/z*): 351.2 (MH^+), R_t: 0.75 min.

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



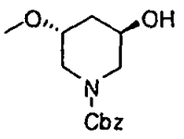
[0120] Following Method 2, tert-butyl (3S,5R)-5-ethyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced to yield tert-butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-ethylpiperidin-3-ylcarbamate. LC/MS (*m/z*): 321.2 (MH^+), R_t: 0.73 min. HPLC: R_t: 2.65 min.

Synthesis of (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-methoxypiperidine-1-carboxylate



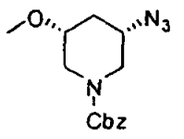
[0121] To a solution of (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-hydroxypiperidine-1-carboxylate (1 eq) in 30 mL of THF was added sodium hydride (1.5 eq) and followed by methyl iodide (5 eq) at 0°C. The reaction mixture was allowed to stir at room temperature for 3 hours. The crude mixture was diluted with 120 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 5) to yield (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-methoxypiperidine-1-carboxylate (93%). LC/MS (*m/z*): 380.2 (MH^+).

Synthesis of (3R,5R)-benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate



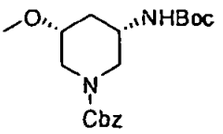
[0122] To a solution of (3R,5R)-benzyl 3-(tert-butyldimethylsilyloxy)-5-methoxypiperidine-1-carboxylate (1 eq) in 30 mL of methanol was added 3.8M HCl in isopropanol (4 eq). The reaction mixture was allowed to stand at room temperature for 3 hours at which point it was concentrated under reduced pressure. The resulting residue was diluted with 100 mL of EtOAc, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 2 : 1) to yield (3R,5R)-benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate (92%). LC/MS (*m/z*): 266.2 (MH^+).

Synthesis of (3S,5R)-benzyl 3-azido-5-methoxypiperidine-1-carboxylate



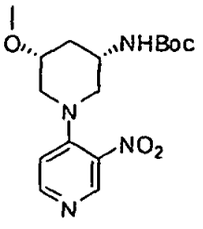
[0123] To a solution of (3R,5R)-benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate (1 eq) in 40 mL of dichloromethane was added triethyl amine (3 eq) and methanesulfonyl chloride (1.5 eq) at 0°C. The reaction mixture was allowed to stir at room temperature for 2 hours. The crude mixture was diluted with 150 mL of EtOAc, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to give the intermediate, which was dissolved in 15 mL of DMF. Sodium azide (3.3 eq) was added and the resulting suspension was stirred at 80°C overnight. The reaction mixture was diluted with 150 mL of EtOAc, washed with water, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 2) to yield (3S,5R)-benzyl 3-azido-5-methoxypiperidine-1-carboxylate (95%). LC/MS (*m/z*): 263.2 (MH^+-28).

Synthesis of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-methoxypiperidine-1-carboxylate



[0124] To a solution of (3S,5R)-benzyl 3-azido-5-methoxypiperidine-1-carboxylate (1 eq) in a mixture of 14 mL of pyridine and 2 mL of ammonium hydroxide was added 1M trimethylphosphine (3 eq) at room temperature. The reaction mixture was stirred at room temperature for 4 hours at which point the solvents were removed under reduced pressure to give a yellow oil. The oil was again dissolved in 100 mL of ethanol and concentrated to remove ammonium hydroxide completely. The residue was dissolved in 16 ml of 1,4-dioxane and 16 mL of sat. aq. $NaHCO_3$ was added. Di-tert-butyl dicarbonate (4 eq) in 8 mL of THF was added dropwise at 0°C. The mixture was allowed to stir at room temperature for 2 hours. The crude mixture was diluted with 300 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to yield (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-methoxypiperidine-1-carboxylate (86%). LC/MS (*m/z*): 365.0 (MH^+).

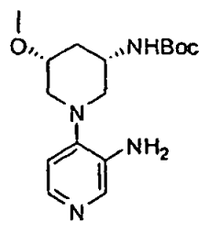
Synthesis of tert-butyl (3S,5R)-5-methoxy-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



[0125] To a solution of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-methoxypiperidine-1-carboxylate (1 eq) in 25 methanol was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere for 2 hours. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo*. The residue was dissolved in 25 mL of isopropanol and

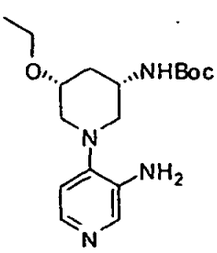
DIEA (1.8 eq) and 4-chloro-3-nitropyridine (1.2 eq) were added. The reaction mixture was stirred at 80°C for 4 hours, at which point the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 150 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5% methanol in EtOAc : hexanes= 1 : 1) to yield (3S,5R)-5-methoxy-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (88%). LC/MS (*m/z*): 353.0 (MH^+). HPLC: R_t: 2.15 min.

Synthesis of tert-Butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-methoxypiperidin-3-ylcarbamate



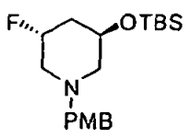
[0126] Following Method 2, tert-butyl (3S,5R)-5-methoxy-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced yielding tert-Butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-methoxypiperidin-3-ylcarbamate. LC/MS (*m/z*): 323.1 (MH^+).

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



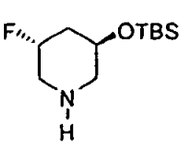
[0127] The procedure to prepare this compound is as same as the methoxy compound. LC/MS (*m/z*): 337.1 (MH^+), R_t: 0.63 min. HPLC: R_t: 2.47 min.

Synthesis of (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoro-1-(4-methoxybenzyl)piperidine



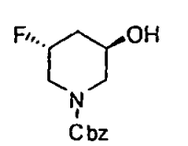
[0128] (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoro-1-(4-methoxybenzyl)-piperidine was prepared according to the literature procedure as described by Cossy, J. *Synlett*, 2007, 263.

Synthesis of (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoropiperidine



[0129] To a solution of (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoro-1-(4-methoxybenzyl)piperidine (1 eq) in 5 mL of methanol was added 10% Pd/C (0.2 eq). The resulting suspension was stirred at H_2 atmosphere overnight. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo* to yield (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoropiperidine, which was used to next step without further purification. LC/MS (*m/z*): 234.1 (MH^+).

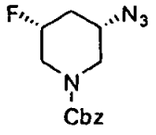
Synthesis of (3R,5R)-benzyl 3-fluoro-5-hydroxypiperidine-1-carboxylate



[0130] To a solution of (3R,5R)-3-(tert-butyldimethylsilyloxy)-5-fluoropiperidine (1 eq) in 30 mL of methanol was added 3.8M HCl in isopropanol (4 eq). The reaction mixture was allowed to stand at room temperature for 3 hours at which point it was concentrated under reduced pressure. The resulting residue was diluted with 120 mL of EtOAc, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous

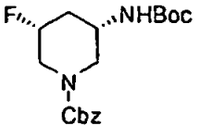
$MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 2 : 1) to give (3R,5R)-benzyl 3-fluoro-5-hydroxypiperidine-1-carboxylate, (94%). LC/MS (*m/z*): 254.2 (MH^+).

Synthesis of (3S,5R)-benzyl 3-azido-5-fluoropiperidine-1-carboxylate



[0131] To a solution of (3R,5R)-benzyl 3-fluoro-5-hydroxypiperidine-1-carboxylate (1 eq) in 14 mL of dichloromethane was added triethyl amine (3 eq) and methanesulfonyl chloride (1.5 eq) at 0°C. The reaction mixture was allowed to stir at room temperature for 1.5 hours. The crude mixture was diluted with 120 mL of diethyl ether, washed with *sat. aq.* sodium bicarbonate, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in 16 mL of NMP. Sodium azide (3.0 eq) was added and the resulting suspension was stirred at 80°C overnight. The reaction mixture was diluted with 200 mL of EtOAc and 100 mL of hexanes, washed with water, brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 3) to yield (3S,5R)-benzyl 3-azido-5-fluoropiperidine-1-carboxylate (90%). LC/MS (*m/z*): 251.1 (MH^+-28).

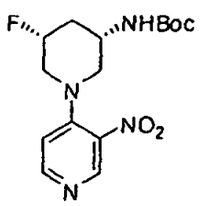
Synthesis of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-fluoropiperidine-1-carboxylate



[0132] To a solution of (3S,5R)-benzyl 3-azido-5-fluoropiperidine-1-carboxylate (1 eq) in a mixture of 11 mL of pyridine and 1.5 mL of ammonium hydroxide was added 1M trimethylphosphine (3 eq) at room temperature. The reaction mixture was stirred at room temperature for 3 hours at which point the solvents were removed under reduced pressure to give a yellow oil. The oil was again dissolved in 100 mL of ethanol and

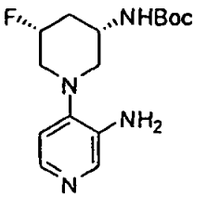
concentrated to remove ammonium hydroxide completely. The residue was dissolved in 12 ml of 1,4-dioxane and 12 mL of sat. aq. $NaHCO_3$ was added. Di-tert-butyl dicarbonate (4 eq) in 6 mL of THF was added dropwise at 0°C. The mixture was allowed to stir at room temperature for 1 hour. The crude mixture was diluted with 150 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to yield (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-fluoropiperidine-1-carboxylate (95%). LC/MS (*m/z*): 253.1 (MH^+-100).

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



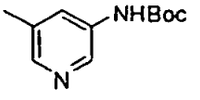
[0133] To a solution of (3S,5R)-benzyl 3-(tert-butoxycarbonylamino)-5-fluoropiperidine-1-carboxylate (1 eq) in 28 methanol was added 10% Pd/C (0.1 eq). The resulting suspension was stirred at H_2 atmosphere for 1 hours. The crude solids were filtered through a pad of Celite on a paper lined Buchner funnel, washed with MeOH, then concentrated *in vacuo*. The residue was dissolved in 33 mL of isopropanol and DIPEA (2.5 eq) and 4-chloro-3-nitropyridine (1.5 eq) were added. The reaction mixture was stirred at 80°C for 2 hours, at which point the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with 150 mL of EtOAc, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5% methanol in EtOAc:hexanes= 1:1) to yield tert-butyl (3S,5R)-5-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (90%). LC/MS (*m/z*): 341.1 (MH^+). HPLC: R_t: 2.12 min.

Synthesis of tert-Butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-fluoropiperidin-3-ylcarbamate



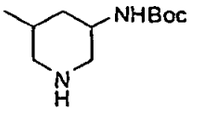
[0134] Following Method 2, tert-butyl (3S,5R)-5-fluoro-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced yielding tert-Butyl (3S,5R)-1-(3-aminopyridin-4-yl)-5-fluoropiperidin-3-ylcarbamate. LC/MS (*m/z*): 311.1 (MH^+).

Synthesis of tert-butyl 5-methylpyridin-3-ylcarbamate



[0135] To a solution of 5-methylpyridin-3-amine (5 g, 46mmol) in THF (80 mL) at r.t. was added 1M sodium bis(trimethylsilylamide) in THF (101 mL, 101 mmol), stirred for 15 min, followed by di-tert-butyldicarbonate(11 g, 49 mmol) in THF (20 mL). The reaction was stirred at r.t overnight and concentrated. The concentrate was treated with 0.2M HCl (60 mL) and EtOAc, and the organic layer was extracted, washed with $NaHCO_{3(sat.)}$ and brine, dried over Na_2SO_4, filtered and concentrated. The concentrate was purified using flash chromatography on silica gel (40% EtOAc : Hexane) to give a yellow solid as product tert-butyl 5-methylpyridin-3-ylcarbamate (8.5 g, 88% yield). LCMS (*m/z*): 209.1 (MH^+); LC R_t = 1.94 min. ^1H NMR($CDCl_3$) δ 8.20(d, 1H), 8.12(s, 1H), 7.86(s, 1H), 6.53(s, 1H), 2.33(s, 3H), 1.53(s, 9H).

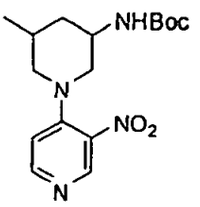
Synthesis of cis-(+/-)-tert-butyl 5-methylpiperidin-3-ylcarbamate



[0136] To a solution of 5-methylpyridin-3-ylcarbamate (3g, 14mmol) in glacial acetic Acid (50 mL) was added 5% Rhodium on active carbon (0.5 g) and Platinum(IV)

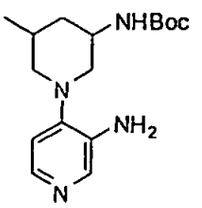
oxide (0.5g) in the hydrogenation steel bomb. The mixture was sealed and hydrogenated at 200 psi and 70 °C for 48 hours. The mixture was filtered through Celite and concentrated to give cis-(+/-)-tert-butyl 5-methylpiperidin-3-ylcarbamate. LCMS (*m/z*): 215.1 (MH^+).

Synthesis of cis-(+/-)-tert-butyl 5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



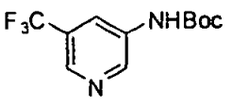
[0137] Method 1 was followed using crude cis-(+/-)-tert-butyl 5-methylpiperidin-3-ylcarbamate yielding cis-(+/-)-tert-butyl 5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate (66 % yield). LCMS (*m/z*): 337.1 (MH^+); LC R_t = 2.50 min. ^1H NMR($CDCl_3$) δ 8.84(s, 1H), 8.36(d, 1H), 7.04(m, 1H), 4.44(m, 1H), 3.90(m, 1H), 3.71(m, 1H), 3.09(d, 1H), 2.66(q, 2H), 2.10(d, 1H), 1.84(m, 1H), 1.56(s, 9H), 0.93(d, 3H).

Synthesis of cis-(+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-methylpiperidin-3-ylcarbamate



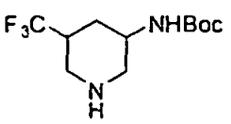
[0138] Method 2 was followed using cis-(+/-)-tert-butyl 5-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate yielding cis-(+/-)-tert-butyl 5-methyl-1-(3-aminopyridin-4-yl)piperidin-3-ylcarbamate (98 % yield). LCMS (*m/z*): 307.1 (MH^+); LC R_t = 2.44 min. ^1H NMR($CDCl_3$) δ 8.01(s, 1H), 7.95(d, 1H), 6.76(d, 1H), 4.40(m, 1H), 3.70(m, 3H), 3.58(dq, 1H), 3.21(dq, 1H), 2.15(m, 3H), 1.90(m, 1H), 1.58(s, 9H), 0.97(d, 3H).

Synthesis of tert-butyl 5-(trifluoromethyl)pyridin-3-ylcarbamate



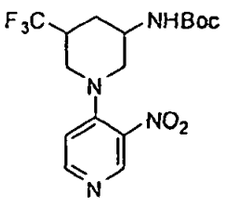
[0139] To a solution of 5-trifluoromethylpyridin-3-amine (1 eq.) in THF (80 mL) at r.t. was added 1M sodium bis(trimethylsilylamide) in THF (2 eq.), stirred for 15 min, followed by di-tert-butyldicarbonate(1eq.) in THF . The reaction was stirred at r.t overnight and concentrated. The concentrate was treated with 0.2M HCl aq. and EtOAc, and the organic layer was extracted, washed with $NaHCO_{3(sat.)}$ and brine, dried over Na_2SO_4, filtered and concentrated. The concentrate was purified using flash chromatography on silica gel (40% EtOAc : Hexane) to give a yellow solid as product tert-butyl 5-(trifluoromethyl)pyridin-3-ylcarbamate (31% yield). LCMS (*m/z*): 263.0 (MH^+); LC R_t = 3.84 min. ^1H NMR($CDCl_3$) δ 8.56(m, 2H), 8.34(s, 1H), 6.71 (s, 1H), 1.55 (s, 9H).

Synthesis of cis-(+/-)-tert-butyl 5-(trifluoromethyl)piperidin-3-ylcarbamate



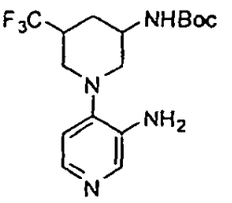
[0140] To a solution of tert-butyl 5-(trifluoromethyl)pyridin-3-ylcarbamate (3g, 14mmol) in glacial acetic acid (50 mL) was added 5% Rhodium on active carbon(0.5 g) and Platinum(IV) oxide (0.5g) in the hydrogenation steel bomb. The mixture was sealed and hydrogenated at 200 psi and 70 °C for 48 h. the mixture was filtered through Celite and concentrated to give cis-(+/-)- tert-butyl 5-(trifluoromethyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 269.1 (MH^+).

Synthesis of cis-(+/-)-tert-butyl 1-(3-nitropyridin-4-yl)-5-(trifluoromethyl)piperidin-3-ylcarbamate



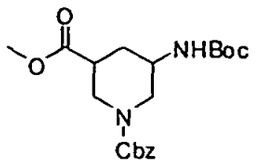
[0141] Method 1 was followed using crude cis-(+/-)-tert-butyl 5-(trifluoromethyl)piperidin -3-ylcarbamate yielding cis-(+/-)-tert-butyl 1-(3-nitropyridin-4-yl)-5-(trifluoromethyl) piperidin-3-ylcarbamate (42% yield over two steps). LCMS (*m/z*): 391.1 (MH^+); LC R_t = 2.92 min. ^1H NMR($CDCl_3$) δ 8.93(s, 1H), 8.47(d, 1H), 7.01(d, 1H), 4.50(m, 1H), 3.80(m, 2H), 3.45(m, 1H), 3.00(t, 1H), 2.66(m, 1H), 2.63(m,1H), 2.38(d, 1H), 1.56(s, 9H).

Synthesis cis-(+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-(trifluoromethyl)piperidin-3-ylcarbamate



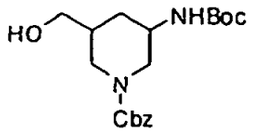
[0142] Method 2 was followed using cis-(+/-)-tert-butyl 1-(3-nitropyridin-4-yl)-5-(trifluoromethyl)piperidin-3-ylcarbamate yielding cis-(+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-(trifluoromethyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 361.0 (MH^+); LC R_t = 2.72 min. ^1H NMR($CDCl_3$) δ 8.05(s, 1H), 7.98(d, 1H), 6.79 (d, 1H), 4.46(m, 1H), 3.83(m, 1H), 3.72(s, 2H), 3.62(m, 1H), 3.49(m, 1H), 2.59(m, 2H), 2.36(m, 1H), 2.23(t,1H), 1.58(s, 9H).

Synthesis of cis (+/-)-1-benzyl 3-methyl 5-(tert-butoxycarbonylamino)piperidine-1,3-dicarboxylate



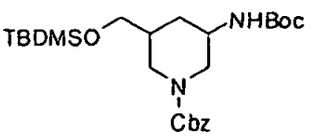
[0143] To a solution of cis (+/-)-1-(benzyloxycarbonyl)-5-(tert-butoxycarbonylamino)piperidine-3-carboxylic acid (1.0eq), methanol (20 eq.) and EDC (1.3 eq) in dichloromethane at a concentration of 0.25 M at 0°C was added dimethylaminopyridine (0.1 eq). After stirring for 48 hours as the reaction was allowed to warm to rt the volatiles were removed in vacuo. Upon addition of ethyl acetate and washing with H_2O (3x), 1N HCl, $NaHCO_{3(sat.)}$ and brine, the solution was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (25% ethyl acetate/hexanes) to yield cis (+/-)-1-benzyl 3-methyl 5-(tert-butoxycarbonylamino)-piperidine-1,3-dicarboxylate. LCMS (*m/z*): 293.1 ($MH\text{-}Boc^+$); LC R_t = 4.09 min

Synthesis of cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(hydroxymethyl)piperidine-1-carboxylate



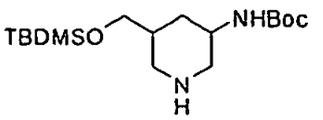
[0144] A solution of cis (+/-)-1-benzyl 3-methyl 5-(tert-butoxycarbonylamino)piperidine-1,3-dicarboxylate (1.0eq.) in THF at a concentration of 0.08 M was cooled at 0° C and then LiCl (2.3 eq.) and sodium borohydride (2.3 eq.) were added. After stirring for 20 hours as the reaction warmed to rt, the pH was adjusted with 1M citric acid to pH 4-5. After removal of the volatiles in vacuo, the product was extracted in dichloromethane, washed with H_2O and brine, dried over $MgSO_4$. Upon filtering and removal of the volatiles in vacuo, cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(hydroxymethyl)piperidine-1-carboxylate was obtained as a white foamy solid. LCMS (*m/z*): 265.0 ($MH\text{-}Boc^+$); LC R_t = 3.37 min.

Synthesis of cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-((tert-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate



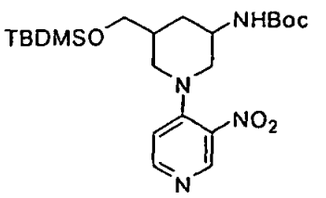
[0145] A solution of cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(hydroxymethyl)piperidine-1-carboxylate (1.0 eq.), imidazole (1.1 eq.), tert-butyldimethylsilylchloride (1.1 eq.) and dimethylaminopyridine (0.1 eq.) in dichloromethane at a concentration of 0.1 M was sirred for 18 hours at which time the volatiles were removed in vacuo. Direct purification of the crude material by column chromatography (20% ethyl acetate/hexanes) yielded cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-((tert-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate. LCMS (*m/z*): 379.0 ($MH\text{-}Boc^+$); LC R_t = 5.95 min.

Synthesis of cis (+/-)-tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)piperidin-3-ylcarbamate



[0146] Method 2 was followed to deprotect cis (+/-)-benzyl 3-(tert-butoxy-carbonylamino)-5-((tert-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate yielding cis (+/-)-tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 344.1 (MH^+).

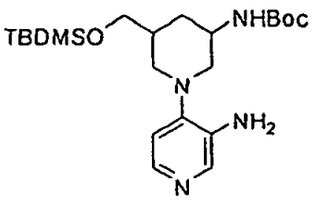
Synthesis of cis (+/-)-tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



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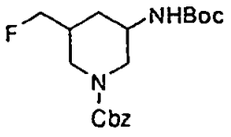
[0147] Method 1 was followed using cis (+/-)-tert-butyl 5-((tert-butyl-dimethylsilyloxy)methyl)piperidin-3-ylcarbamate and 4-chloro-3-nitropyridine yielding cis (+/-)-tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-1-(3-nitropyridin-4-yl)-piperidin-3-ylcarbamate. LCMS (*m/z*): 467.0 (MH^+); LC R_t = 4.02 min.

Synthesis of cis (+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-((tert-butyldimethylsilyloxy)methyl)piperidin-3-ylcarbamate



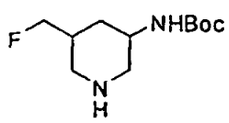
[0148] Following Method 2, cis (+/-)-tert-butyl 5-((tert-butyldimethylsilyloxy)methyl)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced yielding cis (+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-((tert-butyldimethyl-silyloxy)methyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 437.2 (MH^+); LC R_t = 3.86 min.

Synthesis of cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(fluoromethyl)piperidine-1-carboxylate



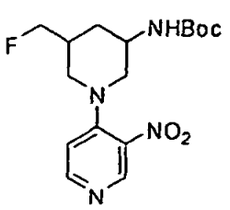
[0149] A solution of cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(hydroxymethyl)piperidine-1-carboxylate (1 eq.), perfluorobutanesulfonylfluoride (2 eq.), triethylamine-HF (4 eq.) and triethylamine (6 eq.) in tetrahydrofuran at a concentration of 0.16 M was stirred for 36 hours. Upon dilution with ethyl acetate (50x) the solution was washed with 1N HCl, $NaHCO_{3(sat.)}$ and brine, was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (25-40% ethyl acetate/hexanes) to yield cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(fluoromethyl)piperidine-1-carboxylate (45% yield). LCMS (*m/z*): 267.1 (MH^+); LC R_t = 4.23 min.

Synthesis of cis (+/-)-tert-butyl 5-(fluoromethyl)piperidin-3-ylcarbamate



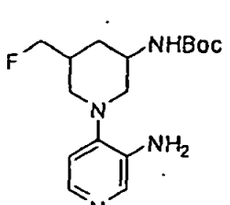
[0150] Method 2 was followed to deprotect cis (+/-)-benzyl 3-(tert-butoxycarbonylamino)-5-(fluoromethyl)piperidine-1-carboxylate yielding cis (+/-)-tert-butyl 5-(fluoromethyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 233.1 (MH^+).

Synthesis of cis (+/-)-tert-butyl 5-(fluoromethyl)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate



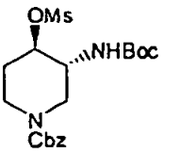
[0151] Method 1 of example 1 was followed using cis (+/-)-tert-butyl 5-(fluoromethyl)piperidin-3-ylcarbamate and 4-chloro-3-nitropyridine yielding cis (+/-)-tert-butyl 5-(fluoromethyl)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate . LCMS (*m/z*): 355.1 (MH^+); LC R_t = 2.41 min.

Synthesis of cis (+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-(fluoromethyl)piperidin-3-ylcarbamate



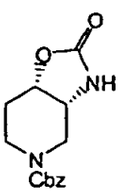
[0152] Following Method 2, cis (+/-)-tert-butyl 5-(fluoromethyl)-1-(3-nitropyridin-4-yl)piperidin-3-ylcarbamate was reduced yielding cis (+/-)-tert-butyl 1-(3-aminopyridin-4-yl)-5-(fluoromethyl)piperidin-3-ylcarbamate. LCMS (*m/z*): 325.1 (MH^+); LC R_t = 2.27 min.

Synthesis of (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(methylsulfonyloxy)piperidine-1-carboxylate



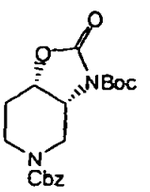
[0153] To a solution of (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate in dichloromethane (0.13 M) was added triethylamine (1.5 equiv.) followed by methanesulfonyl chloride (1.3 equiv.). The reaction was allowed to stir at room temperature for 15 h. The solution was then quenched with saturated $NaHCO_3$, extracted with dichloromethane, dried with sodium sulfate, and concentrated to give the crude (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(methylsulfonyloxy)piperidine-1-carboxylate in >95% yield. LCMS (*m/z*): 428.9/328.9 (MH^+), R_t = 3.81 min.

Synthesis of (3aR,7aS)-benzyl 2-oxohexahydrooxazolo[4,5-c]pyridine-5(6H)-carboxylate



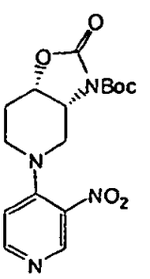
[0154] A solution of (3R,4R)-benzyl 3-(tert-butoxycarbonylamino)-4-(methylsulfonyloxy)piperidine-1-carboxylate in pyridine (0.16 M) was heated to 120 °C in the microwave for 10 minutes. The solution was then concentrated to almost dryness and the forming solid was filtered to give the desired product. The filtrate was further purified via silica gel column chromatography eluting with ethyl acetate (100%) to yield (3aR,7aS)-benzyl 2-oxohexahydrooxazolo[4,5-c]pyridine-5(6H)-carboxylate in 75% combined yield. LCMS (*m/z*): 277.1 (MH^+), R_t = 2.327 min.

Synthesis of (3aR,7aS)-5-benzyl 3-tert-butyl 2-oxotetrahydrooxazolo[4,5-c]pyridine-3,5(2H,6H)-dicarboxylate



[0155] To a solution of (3aR,7aS)-benzyl 2-oxohexahydrooxazolo[4,5-c]pyridine-5(6H)-carboxylate (1.0 equiv.) in dichloromethane (0.09 M) was added BOC_2O (1.1 equiv.), triethylamine (1.1 equiv.), and a catalytic amount of DMAP. The reaction was stirred at room temperature for one hour at which point it was concentrated under vacuo and filtered through a plug of silica gel eluting with ethylacetate. The product was dried under vacuo to yield (3aR,7aS)-5-benzyl 3-tert-butyl 2-oxotetrahydrooxazolo[4,5-c]pyridine-3,5(2H,6H)-dicarboxylate as a white solid in 75% yield. LCMS (*m/z*): 277.2 (MH^+), R_t = 3.43 min.

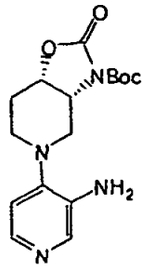
Synthesis of (3aR,7aS)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0156] To a solution of (3aR,7aS)-5-benzyl 3-tert-butyl 2-oxotetrahydrooxazolo[4,5-c]pyridine-3,5(2H,6H)-dicarboxylate in a mixture of EtOH and EtOAc (1:1, 0.07 M) was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen balloon for 15 h. The solution was then filtered through a pad of Celite and the filtrate was concentrated to dryness to give a clear oil. To a solution of (3aR,7aS)-tert-butyl 2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate in i-PrOH (0.12 M)

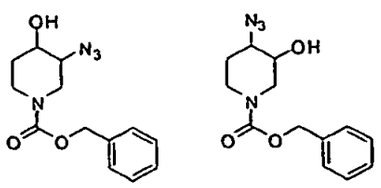
was added 4-chloro-3-nitropyridine (1.2 equiv.) and DIEA (4.0 equiv.) The reaction was heated to 75 °C for 2 h, then cooled to room temperature and concentrated under vacuo. The crude mixture was diluted with EtOAc, water was added, the organic layer was extracted, washed with brine, dried with Na_2SO_4, and concentrated. The crude was purified via silica gel column chromatography eluting with EtOAc (100%) to yield (3aR,7aS)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate as a yellow foam in 89 % yield). LCMS (*m/z*): 365.1 (MH^+), R_t = 1.79 min.

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



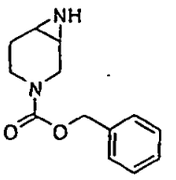
[0157] To a solution of (3aR,7aS)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate in EtOH and EtOAc (1:1, 0.15 M) was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen balloon for 15 h. The solution was filtered through a pad of Celite, and the filtrate was concentrated to yield (3aR,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate as a clear oil in >95% yield. LCMS (*m/z*): 335.0 (MH^+), R_t = 1.68 min.

Synthesis of benzyl 3-azido-4-hydroxypiperidine-1-carboxylate and benzyl 4-azido-3-hydroxypiperidine-1-carboxylate



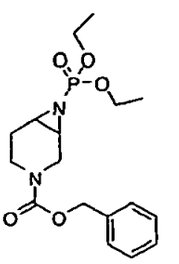
[0158] To a solution of benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (1.0 equiv.) in MeOH and water (0.17M) was added sodium azide (2.0 equiv.) and ammonium chloride (1.0 equiv.). The reaction was stirred at 65°C in an oil bath for 7 h, then concentrated to remove the methanol. Ethyl acetate was added, the organic phase was separated, dried with Na_2SO_4, and concentrated under vacuo to give benzyl 3-azido-4-hydroxypiperidine-1-carboxylate and benzyl 4-azido-3-hydroxypiperidine-1-carboxylate as a clear oil in >95% yield. LCMS (*m/z*): 276.9 (MH^+), R_t = 2.98 min.

Synthesis of benzyl 3,7-diazabicyclo[4.1.0]heptane-3-carboxylate



[0159] To a solution of benzyl 3-azido-4-hydroxypiperidine-1-carboxylate and benzyl 4-azido-3-hydroxypiperidine-1-carboxylate (1.0 equiv.) in dioxane (0.14M) was added PPh_3 (2.0 equiv.) and the reaction was heated to reflux for 1 h. The solution was then concentrated under vacuo and purified via silica gel column chromatography eluting with DCM, 10%MeOH and 1% Et_3N to give benzyl 3,7-diazabicyclo[4.1.0]heptane-3-carboxylate as a clear oil in 25 % yield. LCMS (*m/z*): 233.0 (MH^+), R_t = 1.94 min.

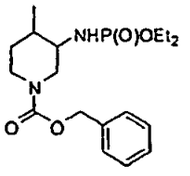
Synthesis of benzyl 7-(diethoxyphosphoryl)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate



[0160] To a solution of benzyl 3,7-diazabicyclo[4.1.0]heptane-3-carboxylate (1.0 equiv.) in DCM (0.26M) was added diethyl phosphorochloridate (1.3 equiv.) and triethyl amine (1.5 equiv.). The reaction was stirred for 24 h, then concentrated to dryness.

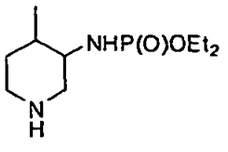
Added water and ethyl acetate, the organics were extracted, dried with Na_2SO_4, and concentrated. The crude was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (50% to 100% ethyl acetate) to yield benzyl 7-(diethoxyphosphoryl)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate as a clear oil in 21% yield. LCMS (*m/z*): 369.0 (MH^+).

Synthesis of benzyl 3-(diethoxyphosphorylamino)-4-methylpiperidine-1-carboxylate



[0161] To a suspension of CuI (0.3 equiv.) in anhydrous THF (0.1M) was added methyl magnesium bromide (3M solution in Et_2O, 10 equiv.) at – 40°C. The reaction was stirred for 30 min, followed by addition of benzyl 7-(diethoxyphosphoryl)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate (1.0 equiv.) in THF (0.1M) at – 40 °C. Allowed the reaction to warm to 10 °C over 5 h, then quenched with water and extracted with ethyl acetate. The organic phase was concentrated under vacuo and purified via silica gel column chromatography eluting with ethyl acetate and hexanes (50% to 100% ethyl acetate) to yield benzyl 3-(diethoxyphosphorylamino)-4-methylpiperidine-1-carboxylate in 35% yield. LCMS (*m/z*): 385.0 (MH^+), R_t = 3.38 min.

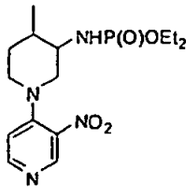
Synthesis of diethyl 4-methylpiperidin-3-ylphosphoramidate



[0162] To a solution of benzyl 3-(diethoxyphosphorylamino)-4-methylpiperidine-1-carboxylate (1.0 equiv.) in degassed MeOH was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen atmosphere for 1 h. The solution was filtered, then

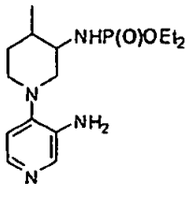
concentrated to yield diethyl 4-methylpiperidin-3-ylphosphoramidate in 83% yield. LCMS (*m/z*): 251.1 (MH^+).

Synthesis of diethyl 4-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate



[0163] To a solution of diethyl 4-methylpiperidin-3-ylphosphoramidate (1.0 equiv.) in isopropyl alcohol was added 4-chloro-3-nitropyridine (2.0 equiv.) and DIEA (1.1 equiv.). The reaction was heated to 70 °C for 18 h, then quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuo. The crude was purified via ISCO (ethyl acetate and hexanes) to yield diethyl 4-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate in 52% yield. LCMS (*m/z*): 373.0 (MH^+), R_t = 1.93 min.

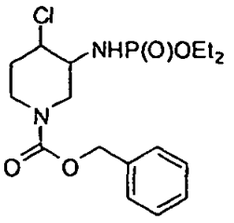
Synthesis of diethyl 1-(3-aminopyridin-4-yl)-4-methylpiperidin-3-ylphosphoramidate



[0164] To a solution of diethyl 4-methyl-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate (1.0 equiv.) in degassed EtOAc (0.1M) was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen atmosphere for 18 h. Filtered and concentrated the filtrate to yield diethyl 1-(3-aminopyridin-4-yl)-4-methylpiperidin-3-ylphosphoramidate in 86% yield. LCMS (*m/z*): 343.0 (MH^+), R_t = 1.85 min.

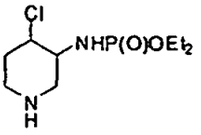
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Synthesis of benzyl 4-chloro-3-(diethoxyphosphorylamino)piperidine-1-carboxylate



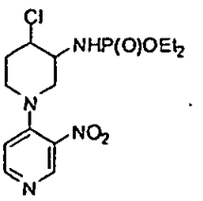
[0165] To a solution of benzyl 7-(diethoxyphosphoryl)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate (1.0 equiv.) and triethyl amine hydrochloride (4 equiv.) in DCM (0.1M) was added $BF_3.OEt_2$ (2.0 equiv.) and the reaction was allowed to stir at room temperature for 2 h under a nitrogen atmosphere. The solution was then quenched with water and extracted with DCM. The crude product was purified via silica gel column chromatography (ISCO eluting with EtOAc and Hexanes 50% to 100% EtOAc) to yield benzyl 4-chloro-3-(diethoxyphosphorylamino)piperidine-1-carboxylate in 89% yield. LCMS (*m/z*): 405.1 (MH^+), R_t = 2.73 min.

Synthesis of diethyl 4-chloropiperidin-3-ylphosphoramidate



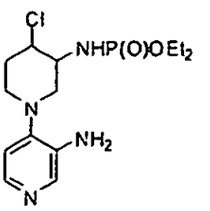
[0166] To a solution of benzyl 4-chloro-3-(diethoxyphosphorylamino)piperidine-1-carboxylate (1.0 equiv.) in degassed MeOH was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen atmosphere for 1 h. The solution was filtered, then concentrated to yield diethyl 4-chloropiperidin-3-ylphosphoramidate in 92% yield. LCMS (*m/z*): 271.0 (MH^+).

Synthesis of diethyl 4-chloro-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate



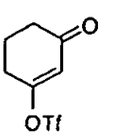
[0167] To a solution of diethyl 4-chloropiperidin-3-ylphosphoramidate (1.0 equiv.) in isopropyl alcohol (0.1M) was added 4-chloro-3-nitropyridine (2.0 equiv.) and DIEA (1.1 equiv.). The reaction was heated to 70°C for 18 h, then quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuo. The crude was purified via ISCO (ethyl acetate and hexanes then 10% methanol in DCM) to yield diethyl 4-chloro-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate in 69% yield. LCMS (*m/z*): 393.1 (MH^+), R_t = 2.01 min.

Synthesis of diethyl 1-(3-aminopyridin-4-yl)-4-chloropiperidin-3-ylphosphoramidate



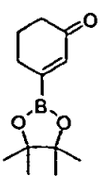
[0168] To a solution of diethyl 4-chloro-1-(3-nitropyridin-4-yl)piperidin-3-ylphosphoramidate (1.0 equiv.) in degassed EtOAc (0.1M) was added Pd/C (10% by weight) and the reaction was stirred under a hydrogen atmosphere for 18 h. Filtered and concentrated the filtrate to yield diethyl 1-(3-aminopyridin-4-yl)-4-chloropiperidin-3-ylphosphoramidate in 83% yield. LCMS (*m/z*): 363.1 (MH^+), R_t = 1.89 min.

Synthesis of 3-oxocyclohex-1-enyl trifluoromethanesulfonate



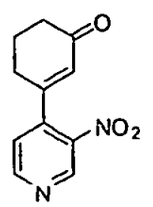
[0169] To a solution of cyclohexane-1,3-dione (1 equiv) in DCM (0.4M) was added Na_2CO_3 (1.0 equiv.) and cooled to 0°C. Added Tf_2O (1.0 equiv.) in DCM (5M) dropwise over 1 hr at room temperature under a nitrogen atmosphere. Upon addition, the reaction was stirred for 2 hr (dark red solution). The solution 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 purified via SiO_2 column chromatography eluting with DCM and hexanes (1:1) or alternatively via a neutral alumina plug eluting with DCM to afford 3-oxocyclohex-1-enyl trifluoromethanesulfonate in 30% or 67% yield respectively. 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



[0170] To a solution of 3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 equiv.) in degassed dioxane (0.3M) 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).

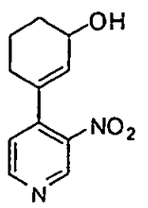
Synthesis of 3-(3-nitropyridin-4-yl)cyclohex-2-enone



[0171] 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-

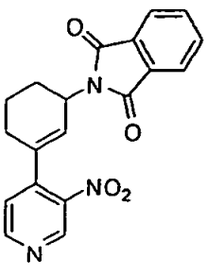
nitropyridine (1.2 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.). The reaction was heated in an oil bath to 120°C for 30 min. (reaction can also be carried out in the microwave for 10 min at 120°C). Cooled to room temperature, then diluted with EtOAc, added H_2O – dark solution, lots of emulsions. Filtered 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 to yield 3-(3-nitropyridin-4-yl)cyclohex-2-enone (64%, 2 steps). LC/MS = 219 (M+H), LC = 2.29 min.

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



[0172] To a solution of 3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 equiv.) was added EtOH (1.1 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 = 2.24 min.

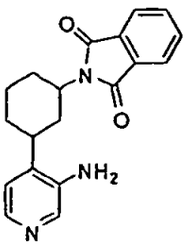
Synthesis of 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione



[0173] To a homogeneous solution of 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

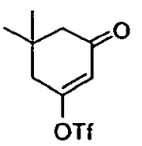
°C, ditertbutyl azodicarboxylate (1.5 eq) in THF was added to the solution. The mixture was stirred at 0 °C for 2 hours. The reaction was concentrated *in vacco*. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give a solid, which was further triturated with DCM and hexanes to yield pure product, plus filtrate. Further purification of the filtrate yielded more pure product. The total yield of 2-(3-(3-nitropyridin-4-yl)cyclohex-2-enyl)isoindoline-1,3-dione is 58%. LC/MS (*m/z*): MH^+=350.2, Rt=0.96. HPLC Rt=3.73.

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



[0174] A solution of 2-(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 (0.15 eq) was added. The reaction mixture was stirred at room temperature for four days 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. Organic layer was dried with $MgSO_4$, filtered, and concentrated. Triturated from EtOAc/hexanes to give 2-(3-(3-aminopyrin-4-yl)cyclohexyl)isoindoline-1,3-dione in 77% yield. LC/MS (*m/z*): MH^+=322.2, Rt=0.64. HPLC Rt=2.43 min.

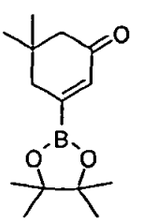
Synthesis of 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate



[0175] 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 equiv.) was added and the

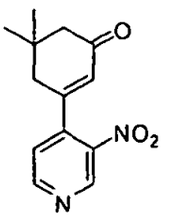
mixture cooled with magnetic stirring on an ice/salt/water bath to ~ -5°C under N_2. Triflic anhydride (1.05 equiv.) diluted in DCM was added drop wise via addition funnel over 90 minutes. Upon completion of addition, the reaction was stirred at ~ 0°C for 1h. From LCMS and ^1H NMR, there was still starting material left. Additional sodium carbonate (0.51 equiv.) and triflic anhydride (0.50 equiv.) 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, concentrated to give 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate, which was used to next step without further purification. LC/MS (*m/z*): MH^+=273.1, Rt=1.03 min.

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



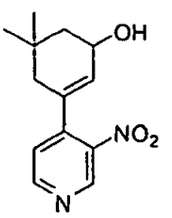
[0176] All of reagents 5,5-dimethyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 eq), potassium acetate (3.0 eq), and bis(pinacolato)diboron (2.0 eq) were added to 1,4-dioxane (0.2 M) in a round bottom flask and degassed by bubbling N_2 through the mixture for 10 min. $PdCl_2(dppf)$ - DCM adduct (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 min.

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



[0177] 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 bottom flask was 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 EtOAc and water. The resulting mixture was filtered through celite, the cake was washed with EtOAc. The organic layer was separated. The aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, 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 min.

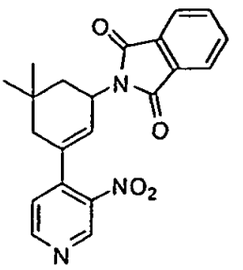
Synthesis of 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



[0178] 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 5mL 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

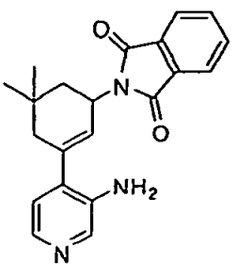
were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column (5% methanol in 1:1 ethyl acetate and hexanes) to give 5,5-dimethyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (74%). LC/MS (*m/z*): MH^+=249.2, Rt=0.76 min.

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



[0179] 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 vacco*. 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 min.

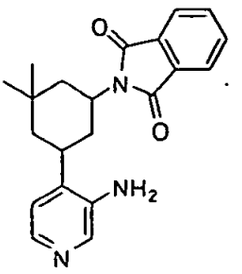
Synthesis of 2-(3-(3-aminopyridin-4-yl)-5,5-dimethylcyclohex-2-enyl)isoindoline-1,3-dione



[0180] 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

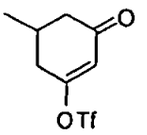
temperature overnight an atmosphere of hydrogen. Solids were removed by filtration over celite, then rinsed with EtOAc and MeOH. The filtrate was concentrated, diluted with EtOAc and washed 2x with sat. aq. 2M Na_2CO_3. Organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was 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 min.

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



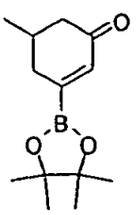
[0181] A solution of 2-(3-(3-aminopyridin-4-yl)-5,5-dimethylcyclohex-2-enyl)isoindoline-1,3-dione (1.0 eq) in acetic acid (0.1 M) was purged with nitrogen for 10 min. Then 10% Pd/C (0.1 eq) was added. The reaction mixture was stirred at 45 °C, 300 psi hydrogen atmosphere in a steel bomb overnight and 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. 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 min. 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 = 7.53 min and 13.11 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 5-methyl-3-oxocyclohex-1-enyltrifluoromethanesulfonate



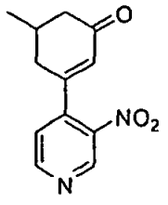
[0182] To a solution of 5-methylcyclohexane-1,3-dione (1 equiv) in DCM (0.4M) was added Na_2CO_3 (1.0 equiv.) and cooled to 0°C. Added Tf_2O (1.0 equiv.) in DCM (5M) dropwise over 1 hr at 0°C under a nitrogen atmosphere. Upon addition, the reaction was stirred for 2 hr at room temperature (dark red solution). 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 purified via SiO_2 column chromatography eluting with DCM and hexanes (1:1) or alternatively via a neutral alumina plug eluting with DCM to afford 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate in 30% or 67% yield respectively. 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 = 0.94 min, LC = 3.84 min.

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



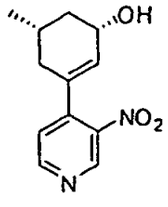
[0183] To a solution of 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 equiv.) in degassed dioxane (0.3M) was added bis(pinacolato)diboron (2.0 equiv.), KOAc (3.0 equiv.), and Pd(dppf)Cl_2-DCM (0.05 equiv.). The reaction was heated to 80°C for 10h, then filtered. The dioxane solution was 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



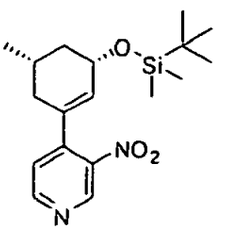
[0184] To a solution of 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (1.0 equiv.) in degassed dioxane and 2M Na_2CO_3 was added 4-chloro-3-nitropyridine (1.2 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.). The reaction was heated in an oil bath to 120°C for 2 h. (reaction can also be carried out in the microwave for 10 min at 120°C). 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 to yield 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone. LC/MS = 233.2 (M+H); Rt = 0.69 min, LC = 2.70 min.

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



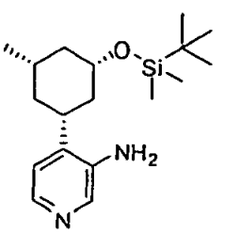
[0185] To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 equiv.) was added EtOH (1.1 M) and $CeCl_3$-$7H_2O$ (1.3 equiv.). The reaction was cooled to 0°C, then $NaBH_4$ (1.3 equiv.) was added in portions. Stirred for 2 h at 0°C, then quenched by adding water, concentrated to remove the EtOH, added EtOAc, extracted the organics, dried with brine, then Na_2SO_4, and concentrated to yield 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (91%). LC/MS = 235.2 (M+H), LC = 2.62 min.

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



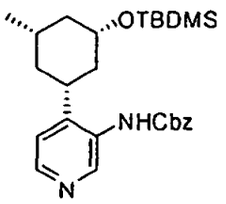
[0186] To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in DMF (0.5 M) was added imidazole (4.0 equiv.) and TBDSMCl (2.5 equiv.). After stirring for 18 hours the solution was portioned between EtOAc and H_2O and separated. After washing further with H_2O (3x) and $NaCl_{(sat.)}$, drying over MgSO4, 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 cis-(+/-)-4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine



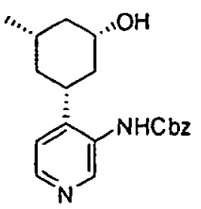
[0187] To a solution of cis--(tert-butyldimethylsilyloxy)-5-methylcyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 15 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding all cis-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



[0188] To a solution of cis-(+/-)-4-(3-(tert-butyldimethylsilyloxy)-5-methylcyclohexyl)pyridin-3-amine in dichloromethane at a concentration of 0.5M 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.

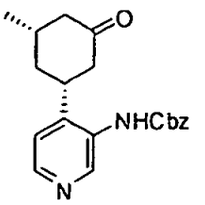
Synthesis of cis-(+/-)benzyl 4-(3-hydroxy-5-methylcyclohexyl)pyridin-3-ylcarbamate



[0189] 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-

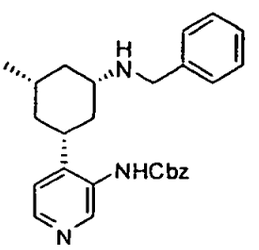
methylcyclohexyl)pyridin-3-ylcarbamate was obtained. The crude material was used as is. LC/MS = 341.2 (M+H), LC = 2.38 min.

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



[0190] To a 0°C solution of cis-(+/-)-benzyl 4-(3-hydroxy-5-methylcyclohexyl)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).

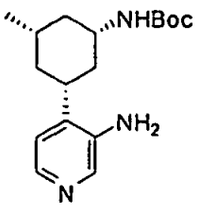
Synthesis of cis-(+/-)- benzyl 4-(-3-(benzylamino)-5-methylcyclohexyl)pyridin-3-ylcarbamate



[0191] 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

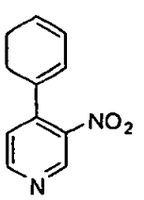
with $NaHCO_{3(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and the after removal of volatiles in vacuo, cis-(+/-)- benzyl 4-(-3-(benzylamino)-5-methylcyclohexyl)pyridin-3-ylcarbamate was obtained as a 4:1 mixture of isomers, with the all cis as predominant LC/MS = 430.3 (M+H), LC = 0.62 min.

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



[0192] 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 silical 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.

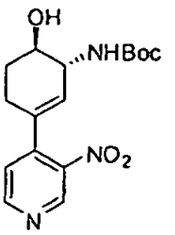
Synthesis of 4-(cyclohexa-1,3-dienyl)-3-nitropyridine



[0193] To a solution of 3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) was added dioxane (0.18M) 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, 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).

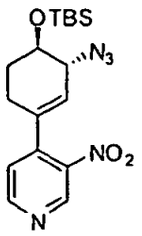
Synthesis of tert-butyl 6-hydroxy-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



[0194] 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

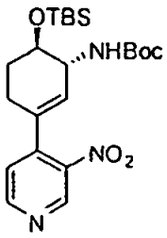
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Synthesis of (+/-)-4-(3-azido-4-(tert-butyldimethylsilyloxy)cyclohex-1-enyl)-3-nitropyridine



[0195] To a solution of (+/-)-2-azido-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in DCM (0.15M) 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 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.

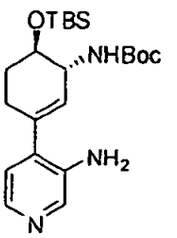
Synthesis of (+/-)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



[0196] In a round-bottomed flask was added (+/-)-4-(3-azido-4-(tert-butyldimethylsilyloxy)cyclohex-1-enyl)-3-nitropyridine (1.0 equiv.) and pyridine (0.1M) 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

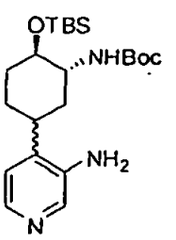
H_2O and EtOAc, the organic phase was dried with $MgSO_4$, filtered and concentrated. The residue was purified via ISCO (5:1 Hex/EtOAc). Collected the pure fractions and concentrated to give (+/-)-tert-butyl 6-(tert-butyldimethylsilyloxy)-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate as a foam. LCMS (*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



[0197] 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



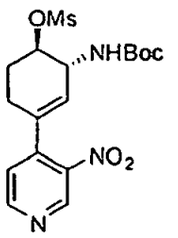
[0198] To a solution of (+/-)-tert-butyl 3-(3-aminopyridin-4-yl)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enylcarbamate (1.0 equiv.) in MeOH (0.1M) was

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.

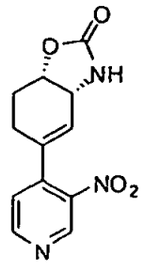
Product B: LCMS (*m/z*): 422.4 (MH^+), LC R_t =3.94 min.

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



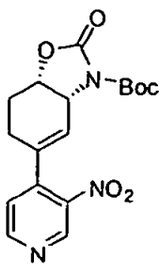
[0199] To a solution of tert-butyl 6-hydroxy-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) and triethyl amine (1.5 equiv.) in CH_2Cl_2 (0.2 M) was added methanesulfonyl chloride (1.2 equiv.) at 0 °C. The mixture was stirred for 2 hours at that temperature. The reaction mixture was diluted 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



[0200] 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

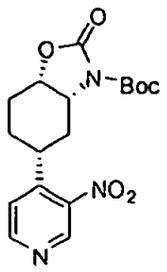
Synthesis of (+/-)-tert-butyl 5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate



[0201] 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-

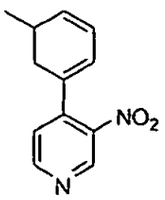
oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (98%). LC/MS (*m/z*): MH^+=306.0, Rt=0.75

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



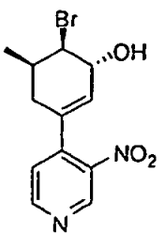
[0202] To a solution of tert-butyl 5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in methanol and ethyl acetate (1;1, 0.1 M) was added Pd/C (10%). The resulting mixture was stirred under H_2 atmosphere for 6 hours. The solid was removed by filtration. 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 (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine



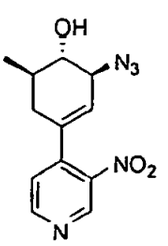
[0203] To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in dioxane (0.1M) was added p-TSA (1.0 equiv.), and the reaction was stirred at 100 °C for 3 h. The solution was cooled to room temperature, then passed through a pad of neutral alumina eluting with EtOAc to yield (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine as a yellow oil in 68% yield. LC/MS = 217.1 (M+H), LC = 3.908 min.

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



[0204] To a solution of 4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine (1.0 equiv.) in THF and water (1:1, 0.13M) 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

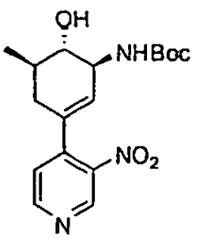


[0205] To a solution of (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in THF (0.1M) was added potassium tert-butoxide (1.5 equiv.). The reaction turned from orange to black almost immediately. By TLC, the formation of product is clean in 30 min. Quenched by adding saturated 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, 0.1M), and ammonium chloride (2.0 equiv) and sodium azide (2.0 equiv.) were added. The dark

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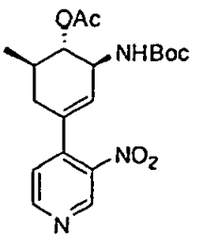
orange reaction was stirred at room temperature overnight. The conversion to product is clean as indicated by LC/MS. The reaction was concentrated to remove the ethanol, ethyl acetate and water were added, the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material 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



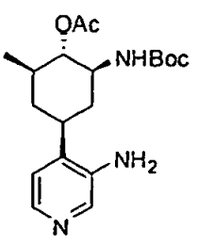
[0206] To a solution of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in pyridine and ammonium hydroxide (8:1, 0.08 M) was added trimethylphosphine (3.0 equiv.) and the brown solution was stirred at room temperature for 2 h. Upon completion, EtOH was added and the solution was concentrated in vacuo. More ethanol was added and the reaction was concentrated again. Dioxane and sat. $NaHCO_3$ (1:1, 0.08M) 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



[0207] To a solution of (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in pyridine (0.1M) was added Ac2O (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.

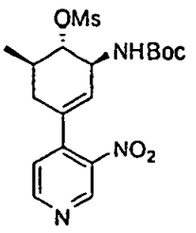
Synthesis of (+/-)-4-(3-aminopyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate



[0208] 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, 0.1M) was added 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

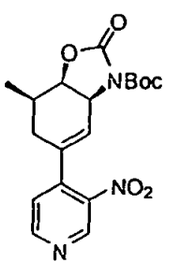
dissolved in ethyl acetate (~20%) and hexanes and heated until all dissolved. The solution was allowed to sit at room temperature for 2 days. The precipitate was then collected to give (+/-)-4-(3-aminopyridin-4-yl)-2-(tert-butoxycarbonylamino)-6-methylcyclohexyl acetate as the pure product in 59% yield. 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



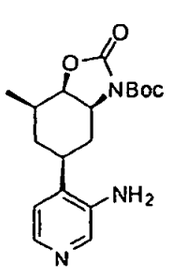
[0209] To a solution of tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in DCM (0.09 M) was added triethylamine (1.5 equiv.) and the reaction was cooled to 0 °C. MsCl (1.2 equiv.) was added to the reaction and stirred for 3 h. Another 1.0 equiv. of MsCl was 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



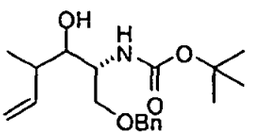
[0210] A solution of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv.) in pyridine (0.2M) was heated in the microwave at 110 °C for 10 min. The orange reaction was then concentrated under vacuo, the crude was dissolved in ethyl acetate and water, the organic phase was dried with sodium sulfate and concentrated under vacuo. The crude material was dissolved in DCM (0.2M), 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



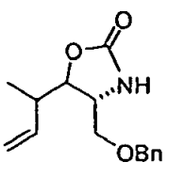
[0211] To a degassed solution of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in MeOH and EtOAc (1:1, 0.1M) was added Pd/C (0.1 equiv.). The reaction was stirred under a hydrogen balloon overnight. Upon completion, the solution 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 tert-butyl (2R)-1-(benzyloxy)-3-hydroxy-4-methylhex-5-en-2-ylcarbamate



[0212] 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.

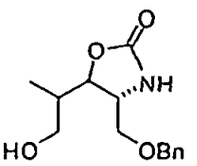
Synthesis of (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one



[0213] 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

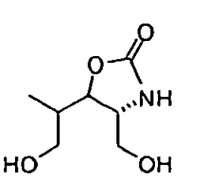
with EtOAc and washed with $NH_4Cl_{(sat.)}$ and $NaCl_{(sat.)}$, dried over $MgSO_4$ and purified by silica gel chromatography (50% EtOAc/hexanes) to yield (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one (89%) as a 3:1 mixture. LCMS (*m/z*): 262.2 (MH^+); LC R_t = 3.47 *min*.

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



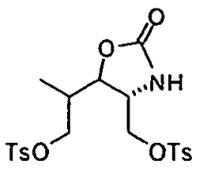
[0214] To a solution of (4R)-4-(benzyloxymethyl)-5-(but-3-en-2-yl)oxazolidin-2-one (1.0 equiv.) in 2:1 MeOH/ H_2O (0.04 M) was added osmium tetroxide 4% in H_2O (0.07 equiv) and sodium periodate (3.0 equiv.). After stirring for 3 hours, the white precipitate was filtered and rinsed with EtOAc. The combined 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



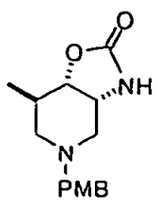
[0215] To a solution of (4R)-4-(benzyloxymethyl)-5-(1-hydroxypropan-2-yl)oxazolidin-2-one (1.0 equiv.) in methanol, at a concentration of 0.1 M, was added 10% palladium on carbon (0.1 eq.). The resultant heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 15 hours. At this 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^+).

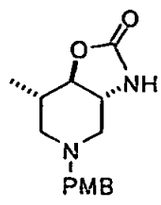
Synthesis of 2-((4R)-2-oxo-4-(tosyloxymethyl)oxazolidin-5-yl)propyl 4-methylbenzenesulfonate



[0216] 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 eluant) 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.

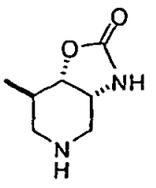
Synthesis of (3aR,7R,7aS)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one and (3aR,7S,7aR)-5-(4-methoxybenzyl)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one





[0217] 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^+).

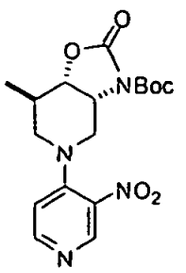
Synthesis of (3aR,7R,7aS)-7-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one



[0218] 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-methylhexahydrooxazolo[4,5-c]pyridin-2(3H)-one (99%). LCMS (*m/z*): 157.1 (MH^+).

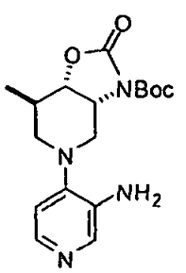
60

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



[0219] 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^+).

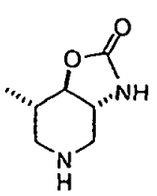
Synthesis of (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0220] 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

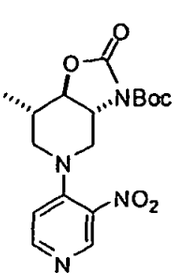
heterogeneous solution was put under an atmosphere of hydrogen and was stirred for 14 hours. At this time the mixture was filtered through a pad of celite eluting with methanol. The volatiles were removed *in vacuo* yielding (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate. 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



[0221] 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^+).

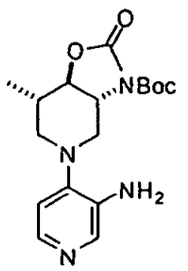
Synthesis of (3aR,7S,7aR)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0222] 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 eluant) 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.

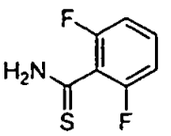
Synthesis of (3aR,7R,7aS)-tert-butyl 5-(3-aminopyridin-4-yl)-7-methyl-2-oxohexahydrooxazolo[4,5-c]pyridine-3(2H)-carboxylate



[0223] 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.

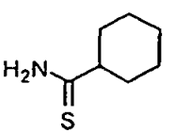
METHOD 3

Synthesis of 2,6-difluorobenzothioamide



[0224] A solution of 2, 6 difluorobenzamide (1 eq) and Lawesson's reagent (0.5 eq.) in toluene (0.2 M) was heated at 90°C for 14 hours. Upon cooling the volatiles were removed in vacuo and purified by SiO_2 chromatography (25% EtOAc/hexanes) yielding 2,6-difluorobenzothioamide as a light yellow solid (99%). LCMS (*m/z*): 174.1 (MH^+); LC R_t = 2.19 min.

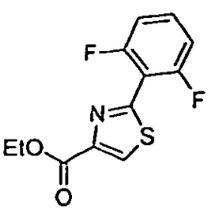
Synthesis of cyclohexanecarbothioamide



[0225] Following Method 3, cyclohexanecarboxamide and Lawesson's reagent were reacted, yielding cyclohexanecarbothioamide. LCMS (*m/z*): 144.1 (MH^+); LC R_t = 5.10 min.

METHOD 4

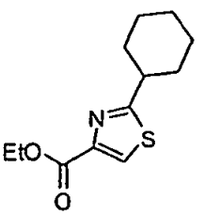
Synthesis of ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate



[0226] A solution of 2,6-difluorobenzothioamide (1.0 eq) and ethylbromopyruvate (1.0 eq.) in ethanol (1.0 M) was heated in the microwave at 130 °C for 30 minutes. Upon removal of volatiles in vacuo, ethyl acetate was added and the

solution was washed with $Na_2CO_{3(sat.)}$, with $NaCl_{(sat.)}$, was dried over $MgSO_4$, filtered and concentrated yielding ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate (84%). LCMS (*m/z*): 270.1 (MH^+); LC R_t = 3.79 min.

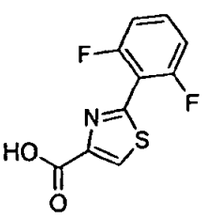
Synthesis of ethyl 2-cyclohexylthiazole-4-carboxylate



[0227] Following Method 4, cyclohexanecarbothioamide was used to yield ethyl 2-cyclohexylthiazole-4-carboxylate. LCMS (*m/z*): 240.1 (MH^+); LC R_t = 3.90 min.

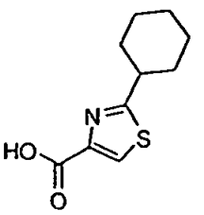
METHOD 5

Synthesis of 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



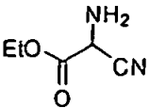
[0228] To a solution of ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate (1.0 eq.) in 2:1 THF/MeOH (0.17 M) was added 1.0 M LiOH (2.0 eq.). After standing for 16 hours, 1.0 M HCl (2.0 eq.) was added and the THF/MeOH was removed in vacuo. The resulting solid was filtered, rinsed with H_2O and dried, yielding 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (88%) as a crusty solid. LCMS (*m/z*): 251.1 (MH^+); LC R_t = 2.68 min.

Synthesis of 2-cyclohexylthiazole-4-carboxylic acid



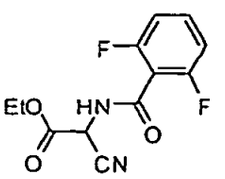
[0229] Following Method 5, ethyl 2-cyclohexylthiazole-4-carboxylate was hydrolyzed yielding 2-cyclohexylthiazole-4-carboxylic acid. LCMS (*m/z*): 212.1 (MH^+); LC R_t = 2.90 min.

Synthesis of ethyl 2-amino-2-cyanoacetate



[0230] To a solution of ethyl 2-cyano-2-(hydroxyimino)acetate(1eq) in 70 mL of water and 56 mL of *aq. sat.* sodium bicarbonate was added portionwise throughout 10 minutes $Na_2S_2O_4$ (2.8 eq) The reaction mixture was stirred at room temperature for 1 hour. The solution was saturated with sodium chloride, extracted with methylene chloride (300mL x 3) and then the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the titled compound, which was used to next step without further (55%). LC/MS (*m/z*): 129.0 (MH^+), R_t: 0.25 min.

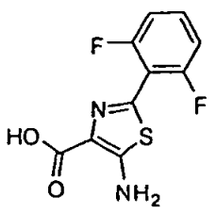
Synthesis of ethyl 2-cyano-2-(2,6-difluorobenzamido)acetate



[0231] To a solution of ethyl 2-amino-2-cyanoacetate (1 eq) in 6 mL of dichloromethane was added pyridine (1.5 eq) and 2,6-difluorobenzoyl chloride (1 eq) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The mixture was diluted with ethyl acetate, washed with brine, then dried over anhydrous $MgSO_4$, filtered,

and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to give the titled compound (84%). LC/MS (*m/z*): 269.1 (MH^+), R_t: 0.69 min.

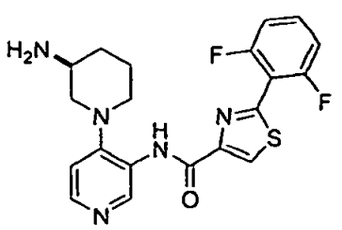
Synthesis of 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



[0232] To a solution of the ethyl 2-cyano-2-(2,6-difluorobenzamido)acetate (1 eq) in 10 mL of toluene was added Lawesson reagent. The mixture was stirred at 95°C for 2 days. Solvents were removed under reduced pressure. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to give the ethyl 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylate, which was dissolved in 5 mL of methanol and 5 mL of THF. Then the mixture was added 1M sodium hydroxide (2eq). The reaction mixture was stirred at room temperature overnight. The reaction was concentrated to remove most of solvents. The residue was extracted with ethyl acetate. The aqueous layer was acidified to pH = 4-5 by 1N HCl. The resulting mixture was extracted by ethyl acetate. The organic layer was separated, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. to give the pure titled compound (34%). LC/MS (*m/z*): 257.1 (MH^+), R_t: 0.61 min.

METHOD 6

Synthesis of (S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide



[0233] A homogeneous solution of 1 eq each of (S)-tert-butyl 1-(3-aminopyridin-4-yl)piperidin-3-ylcarbamate, 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid, HOAT and EDC in NMP, at a concentration of 0.38 M, was left standing for 48 hours at which time the mixture was directly purified by HPLC. Upon lyophilization, the TFA salt of (S)-tert-butyl 1-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)piperidin-3-ylcarbamatewas 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*, (S)-tert-butyl 1-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)piperidin-3-ylcarbamate was obtained.

[0234] The Boc group was removed by treating with 25% TFA/CH_2Cl_2 for 2 hours or with excess 4M HCl in dioxane for 12 hours. Upon removal of the volatiles *in vacuo*, the material was purified by RP HPLC yielding after lyophilization (S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide 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 (S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide was obtained (43 %). LCMS (*m/z*): 416.1 (MH^+); LC R_t = 1.95 min.

[0235] If benzoyl protected hydroxyls were present they could be deprotected prior to Boc removal by treating with 0.2 M sodium hydroxide (3 eq) in MeOH at room temperature for 3 hours, upon which time the solution was diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield the Boc protected alcohol.

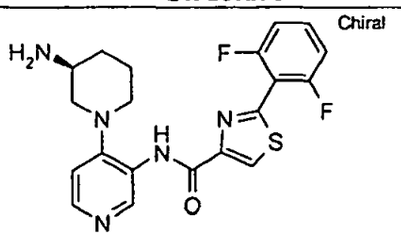
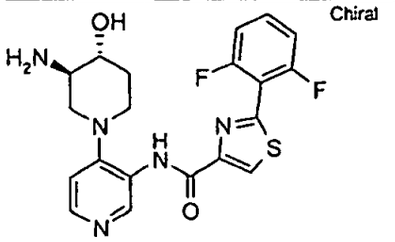
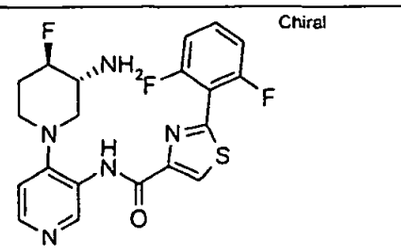
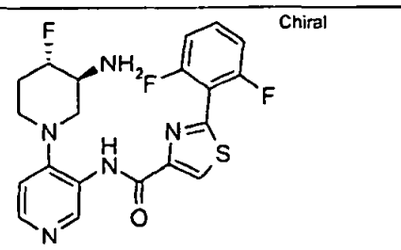
[0236] If an N-Boc1,2 amino alcohol cyclic carbamate was present, prior to Boc deprotection the cyclic carbamate could be cleaved by treating with Cs_2CO_2 (0.5 eq) in methanol at a concentration of 0.1 M for three hours. After removal of volatiles *in vacuo*, the Boc amino group was deprotected as described above.

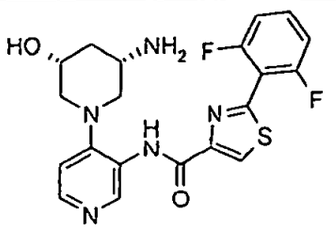
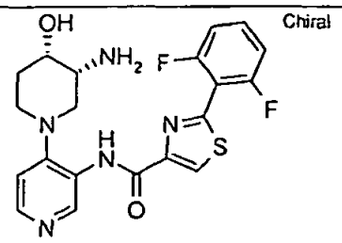
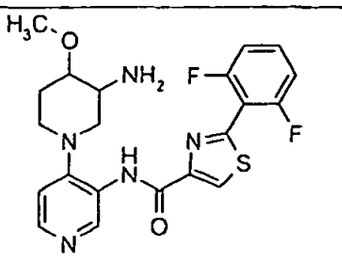
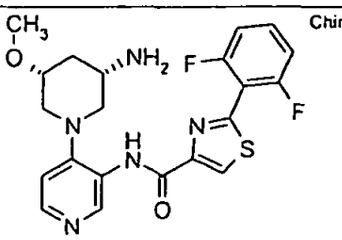
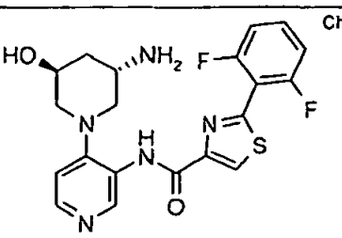
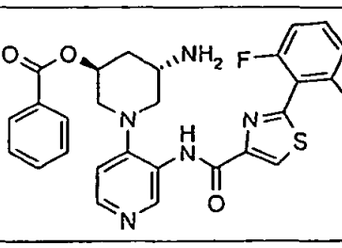
[0237] If TBDMS ethers were present they were deprotected prior to Boc removal by treating with 6N HCl, THF, methanol (1:2:1) at room temperature for 2 h. After removal of volatiles *in vacuo*, the Boc amino group was deprotected as described above.

[0238] If a diethoxyphosphorylamino group was present, the amine was deprotected by heating in a 1:1 solution of dioxane/ 2N $HCl_{(aq.)}$ at 70°C overnight. Upon removal of the volatiles *in vacuo*, the material was purified by RP HPLC.

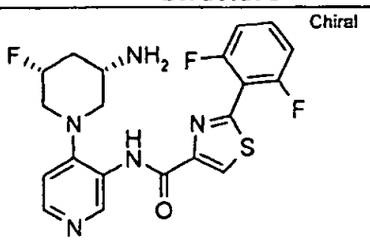
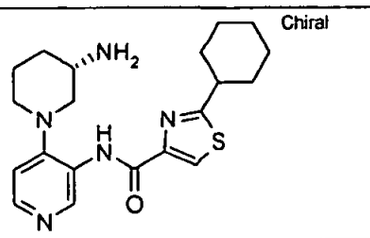
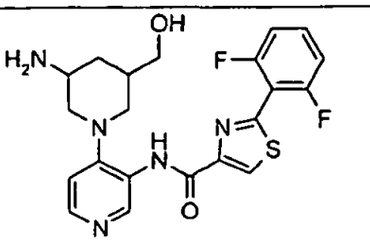
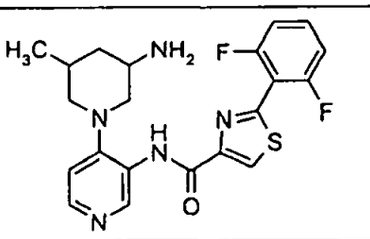
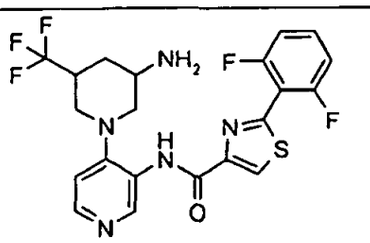
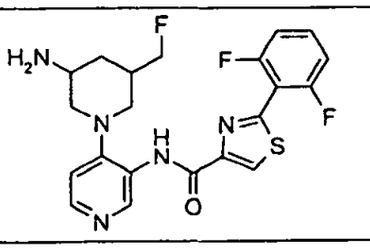
[0239] The following compounds were prepared using Method 6:

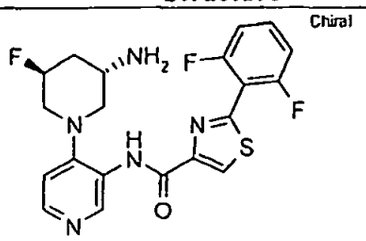
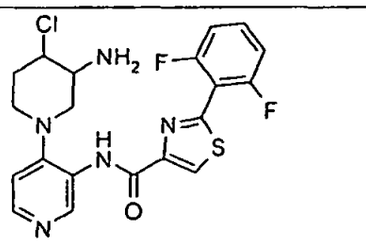
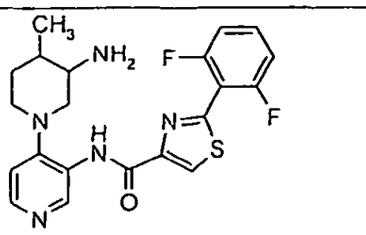
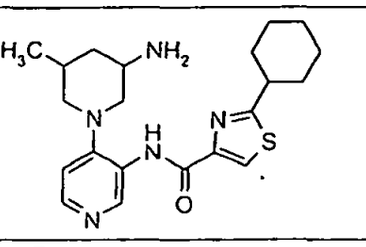
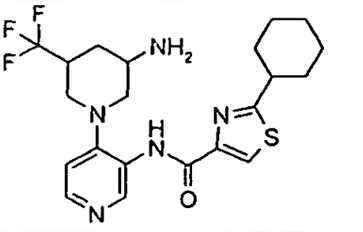
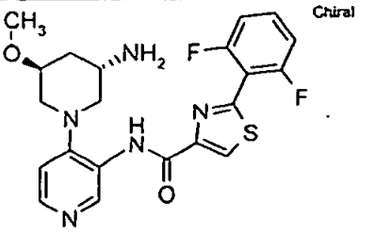
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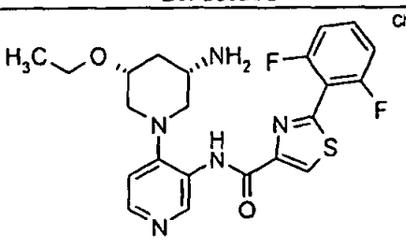
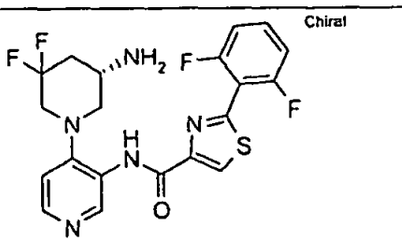
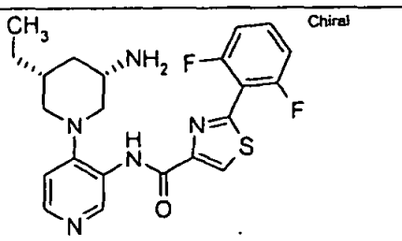
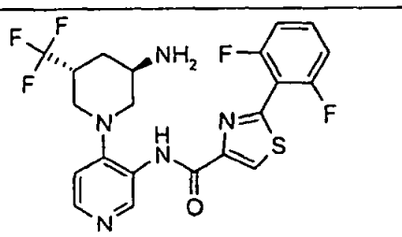
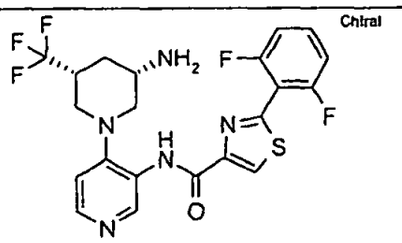
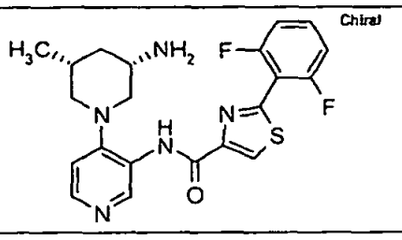
Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
1	 Chiral	(S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)- 2-(2,6-difluorophenyl)thiazole-4-carboxamide	416.1	1.95
2	 Chiral	N-(4-((3R,4R)-3-amino-4-hydroxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	432.1	1.84
3	 Chiral	N-(4-((3R,4R)-3-amino-4-fluoropiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	434.1	2.23
4	 Chiral	N-(4-((3S,4S)-3-amino-4-fluoropiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	434.1	2.22

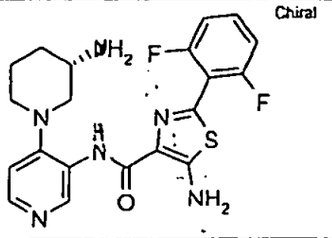
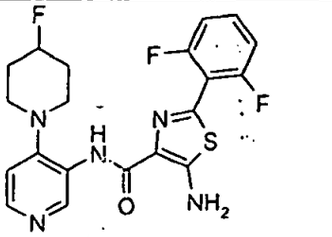
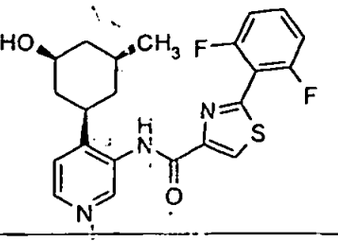
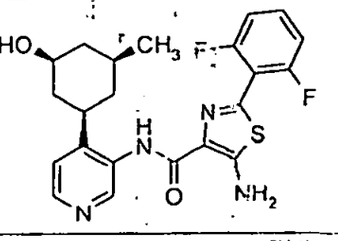
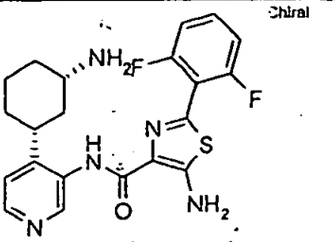
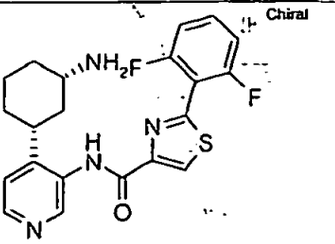
Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
5		N-(4-((3S,5R)-3-amino-5-hydroxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	432	1.65
6	 Chiral	N-(4-((3R,4S)-3-amino-4-hydroxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	432.1	1.89
7		N-(4-(3-amino-4-methoxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	445.9	1.96
8	 Chiral	N-(4-((3S,5R)-3-amino-5-methoxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl) thiazole-4-carboxamide	446.1	1.83
9	 Chiral	N-(4-((3S,5S)-3-amino-5-hydroxypiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	432.0	1.75
10	 Chiral	(3S,5S)-5-amino-1-(3-(2-(2,6-difluorophenyl) thiazole-4-carboxamido)pyridin-4-yl) piperidin-3-yl benzoate	536.1	2.44

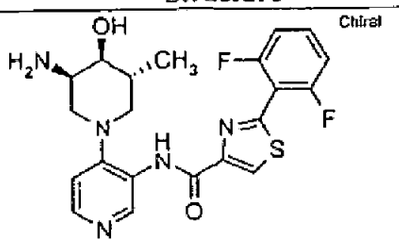
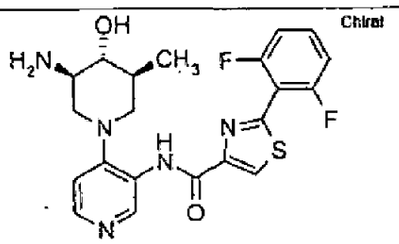
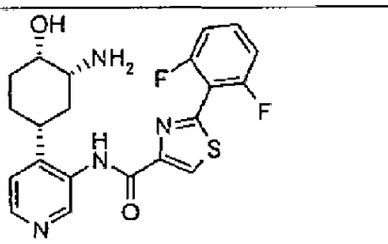
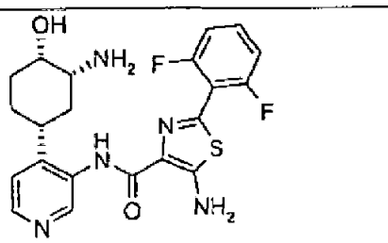
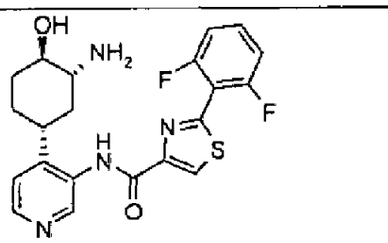
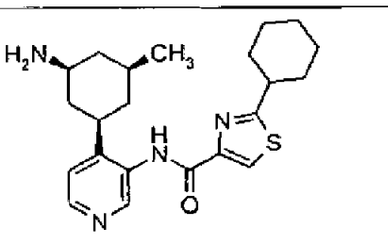
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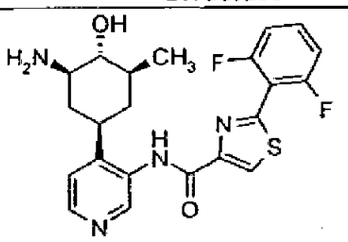
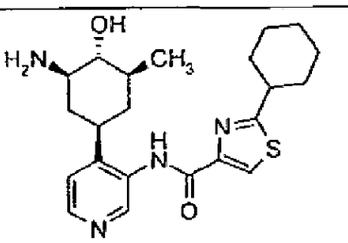
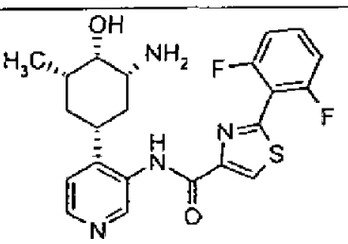
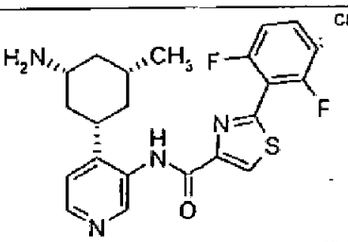
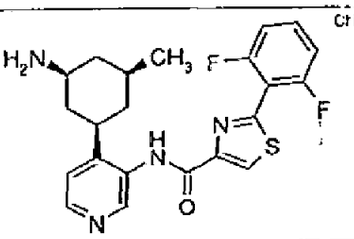
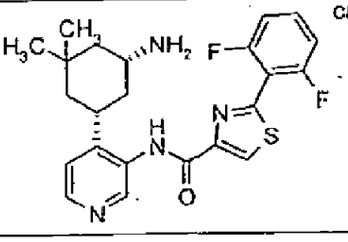
Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
11		N-(4-((3S,5R)-3-amino-5-fluoropiperidin-1-yl) pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	433.9	1.80
12		(S)-N-(4-(3-aminopiperidin-1-yl) pyridin-3-yl)-2-cyclohexylthiazole-4-carboxamide	386.1	2.12
13		N-(4-(3-amino-5-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	446.0	1.78
14		N-(4-(3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	430.0	2.14
15		N-(4-(3-amino-5-(trifluoromethyl) piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	484.1	2.27
16		N-(4-(3-amino-5-(fluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl) thiazole-4-carboxamide	448.0	2.05

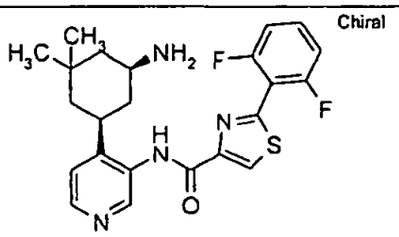
Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
17	 Chiral	N-(4-((3S,5S)-3-amino-5-fluoropiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	434.0	0.49
18		N-(4-(3-amino-4-chloropiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	449.8	0.55
19		N-(4-(3-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	430.1	0.57
20		N-(4-(3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-cyclohexylthiazole-4-carboxamide	400.1	0.64
21		N-(4-(3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-cyclohexylthiazole-4-carboxamide	454.1	0.72
22	 Chiral	N-(4-((3S,5S)-3-amino-5-methoxypiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	446.1	0.54

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
23	 Chiral	N-(4-((3S,5R)-3-amino-5-ethoxypiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	460.0	0.54
24	 Chiral	(S)-N-(4-(5-amino-3,3-difluoropiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	452.0	0.56
25	 Chiral	N-(4-((3S,5R)-3-amino-5-ethylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	444.1	0.57
26		N-(4-((3R,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	484.1	0.57
27	 Chiral	N-(4-((3S,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	484.0	0.68
28	 Chiral	N-(4-((3S,5R)-3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	430.2	0.60

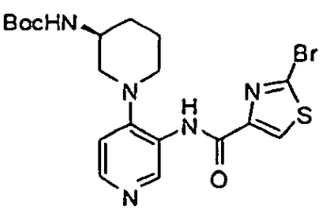
Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
29		(S)-5-amino-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	431.0	0.51
30		5-amino-2-(2,6-difluorophenyl)-N-(4-(4-fluoropiperidin-1-yl)pyridin-3-yl)thiazole-4-carboxamide	434.0	0.75
31		2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide	430.1	0.7
32		5-amino-2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide	445.1	0.7
33		5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	430.0	0.54
34		N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	415.0	0.54

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
35		N-(4-((3R,4S,5R)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	446.2	0.51
36		N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	446.0	0.55
37		N-(4-((1R,3R,4S)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	431.0	0.50
38		5-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	446.1	0.51
39		N-(4-((1R,3R,4R)-3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	431.0	0.54
40		N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-cyclohexylthiazole-4-carboxamide	399.3	0.63

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
41		N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (and enantiomer)	445.1	0.52
42		N-(4-((1R,3R,4R,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-2-cyclohexylthiazole-4-carboxamide	415.1	0.60
43		N-(4-((1R,3R,4S,5S)-3-amino-4-hydroxy-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (and enantiomer)	445.2	0.54
44		N-(4-((1S,3R,5R)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	429.2	0.68
45		N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	429.2	0.68
46		N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	443.2	0.60

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
47		N-(4-((1R,5R)-5-amino-3,3-dimethylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	443.2	0.60

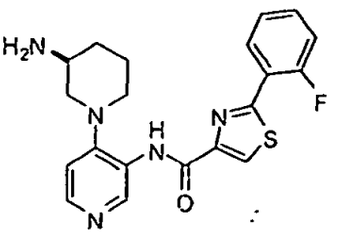
Synthesis of (S)-tert-butyl 1-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)piperidin-3-ylcarbamate



[0240] A solution containing 1 eq each of (S)-tert-butyl 1-(3-aminopyridin-4-yl)piperidin-3-ylcarbamate, 2-bromothiazole-4-carboxylic acid, HOAT and EDC in DMF, at a concentration of 0.5 M, was stirred for 60 hours. The solution was diluted with EtOAc and was washed with H_2O (4x), $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and the volatiles were removed *in vacuo* yielding (S)-tert-butyl 1-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)piperidin-3-ylcarbamate, LCMS (*m/z*): 416.1 (MH^+); LC R_t = 1.95 min.

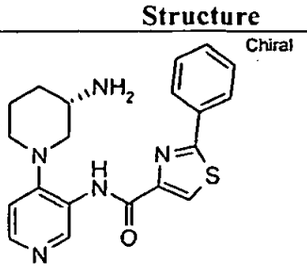
METHOD 7

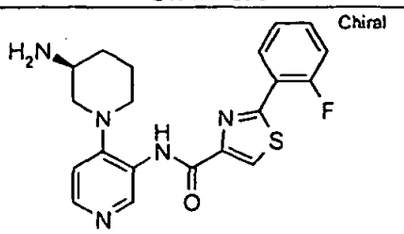
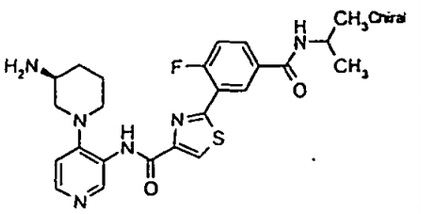
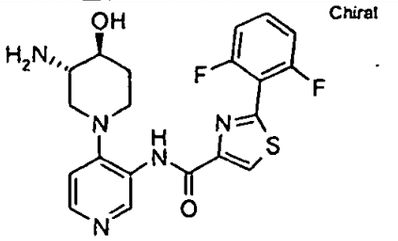
Synthesis of (S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide



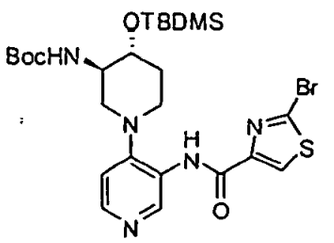
[0241] A solution of (S)-tert-butyl 1-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)piperidin-3-ylcarbamate (1.0 eq), 2-fluorophenyl boronic acid (3.0 eq.), $Pd(dppf)Cl_2$-CH_2Cl_2 (0.15 eq.) in 3:1 DME/2M Na_2CO_3 (concentration = 0.1 M) was heated at 120°C with microwave irradiation for 1200 seconds. Upon cooling the organic layer was separated, concentrated and the N-Boc Suzuki product was directly purified by reverse phase HPLC. The product fraction was lyophilized and the resulting solid was treated with 25% TFA/DCM (at a resulting concentration of 0.05 M). After sitting for 2 hours, the volatiles were removed *in vacuo* and the residue was purified by reverse phase HPLC. After lyophilization, (S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide was obtained (35%) as the TFA salt. LCMS (m/z): 398.1 (MH+); LC Rt = 2.06 min.

[0242] The following compounds were prepared using Method 7:

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
48		(S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-phenylthiazole-4-carboxamide	380.1	1.94

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
49		(S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2-fluorophenyl) thiazole-4-carboxamide	398.1	2.06
50		(S)-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2-fluoro-5-(isopropylcarbamoyl) phenyl)thiazole-4-carboxamide	483.2	2.04
51		N-(4-((3S,4S)-3-amino-4-hydroxy-piperidin-1-yl) pyridin-3-yl)-2-(2,6-difluoro phenyl)thiazole-4-carboxamide	432.1	1.85

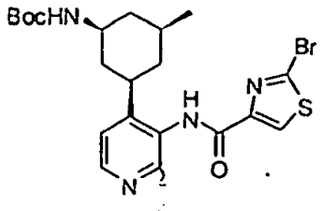
Synthesis of tert-butyl (3R,4R)-1-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate



[0243] A solution containing 1 eq each of tert-butyl (3R,4R)-1-(3-aminopyridin-4-yl)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, 2-bromothiazole-4-carboxylic acid, HOAT and EDC in DMF, at a concentration of 0.5 M, was stirred for 60 hours. The solution was diluted with EtOAc and was washed with H_2O (4x), $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and the volatiles were removed *in vacuo* yielding

tert-butyl . (3R,4R)-1-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)-4-(tert-butyldimethylsilyloxy)piperidin-3-ylcarbamate, LCMS (*m/z*): 612.2/614.2 (MH^+); LC R_t = 4.26 min.

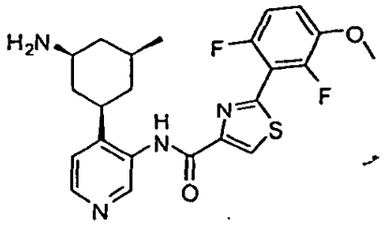
Synthesis of tert-butyl (1S,3R,5S)-3-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)-5-methylcyclohexylcarbamate



[0244] A solution containing 1 eq each of tert-butyl (1S,3R,5S)-3-(3-aminopyridin-4-yl)-5-methylcyclohexylcarbamate, 2-bromothiazole-4-carboxylic acid, HOAT and EDC in DMF, at a concentration of 0.3 M, was stirred for 17 hours. The solution was diluted with EtOAc and was washed with H_2O (4x), $NaCl_{(sat.)}$, was dried over $MgSO_4$, was filtered and the volatiles were removed *in vacuo* yielding tert-butyl (1S,3R,5S)-3-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)-5-methylcyclohexylcarbamate, LCMS (*m/z*): 495.1/497.1 (MH^+); LC R_t = 3.17 min.

METHOD 8

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



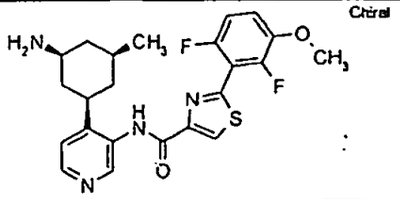
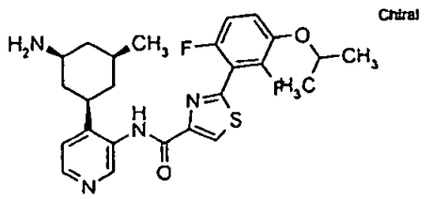
[0245] A solution of tert-butyl (1S,3R,5S)-3-(3-(2-bromothiazole-4-carboxamido)pyridin-4-yl)-5-methylcyclohexylcarbamate (1.0 equiv.), 2,6-difluoro-3-methoxyphenylboronic acid (4.0 equiv.), DIEA (4.0 equiv.) and $Pd(PPh_3)_4$ (0.2 equiv) in 1:1 toluene/ethanol at a concentration of 0.03 M was heated in a microwave at 120°C for

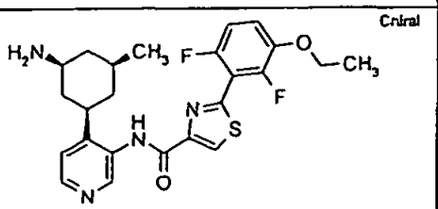
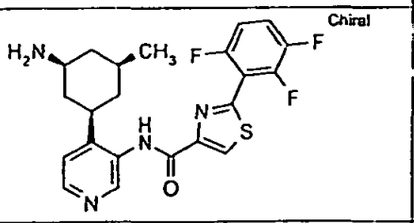
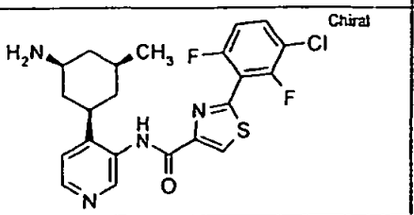
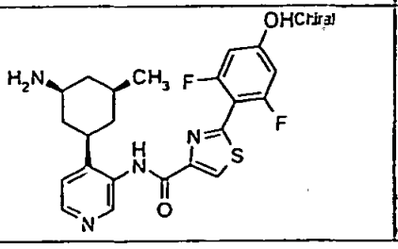
20 minutes. The solution was resubmitted to heating in the microwave at 130°C for 2x30 min. The solvents were removed in vacuo and the residue was purified by HPLC. The product fractions were lyophilized directly to yield the protected amide product as the TFA salt. The Boc group was deprotected by treating with 25% TFA/CH_2Cl_2 for two hours. Upon removal of volatiles in vacuo, the product was purified by HPLC to yield N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide. LCMS (*m/z*): 459.2 (MH^+); LC R_t = 2.32 min.

[0246] When applying the above method for Suzuki it is at times necessary to resubmit to heating in the microwave and additionally add more of the boronic acid (4.0 equiv.), DIEA (4.0 equiv.) and $Pd(PPh_3)_4$ (0.2 equiv) with each resubmission.

[0247] Alternatively, Suzuki reactions with 2,6 difluorosubstituted boronic acids and 2-bromo-4-carboxamido thiazoles can be carried out by heating the bromide (1.0 equiv), boronic acid (5 equiv.), KF (5.5 equiv.), tri-tert-butylphosphine (0.4 equiv) and $Pd_2(dba)_3$ (0.2 equiv.) in 10:1 THF/H_2O at a concentration of 0.03 M in the microwave at 100°C for 30 minutes. With this method, is at times necessary to resubmit to heating in the microwave at 100°C and additionally add more of the boronic acid (5.0 equiv.), KF (5.5 equiv.), tri-tert-butylphosphine (0.4 equiv) and $Pd_2(dba)_3$ (0.2 equiv.) with each resubmission.

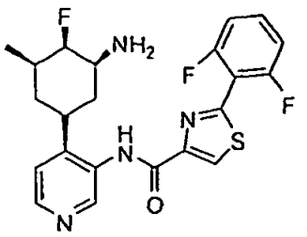
[0248] The following compounds were prepared using Method 8:

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
52	 Chiral	2-(2,6-Difluoro-3-methoxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide	459.2	0.58
53	 Chiral	2-[2-Fluoro-1-(1-fluoro-vinyl)-3-isopropoxy-propenyl]-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-	487.3	0.67

Ex. No.	Structure	Compound Name	LC/MS (M+H on UPCL)	LC/MS (Rf min on UPLC)
		3-yl]-amide		
54		2-(3-Ethoxy-2,6-difluoro-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide	473.3	0.63
55		2-(2,3,6-Trifluoro-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide	447.2	0.59
56		2-(3-Chloro-2,6-difluoro-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide	463.1	0.62
57		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide	445.2	0.54

Example 58

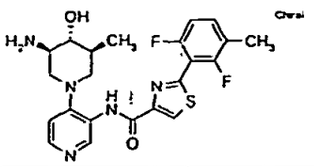
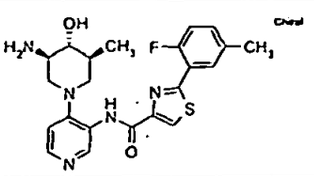
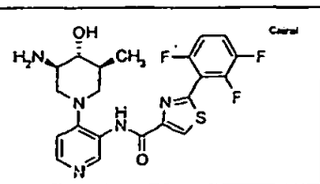
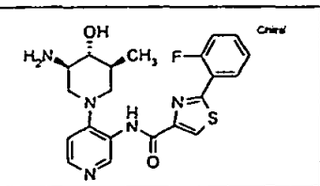
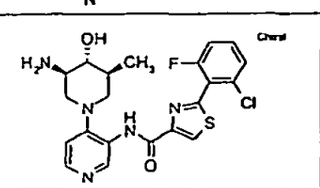
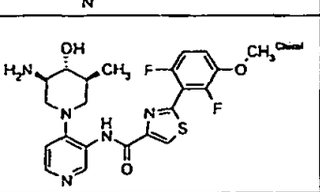
Synthesis of N-(4-((+/-)-3-amino-4-fluoro-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

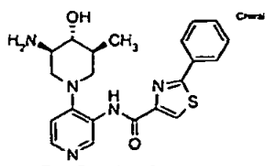
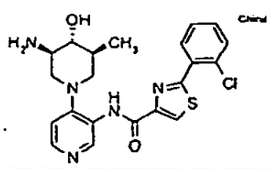
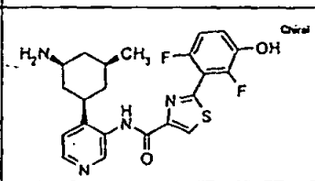
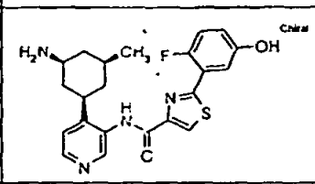
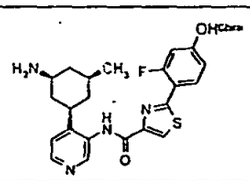
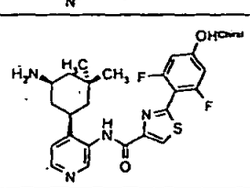
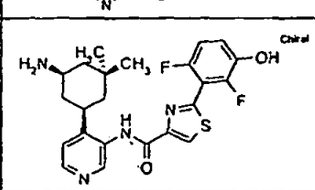
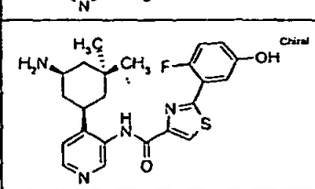


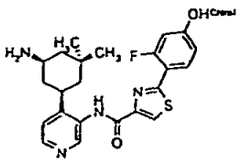
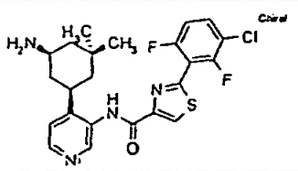
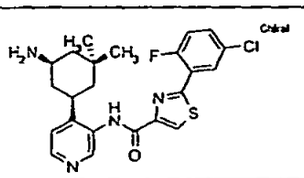
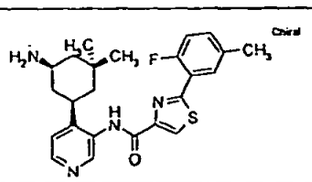
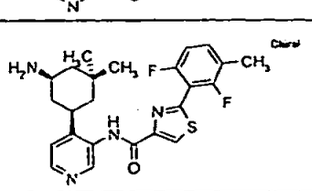
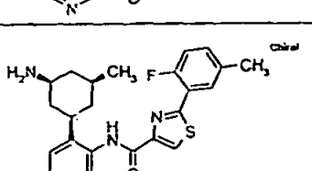
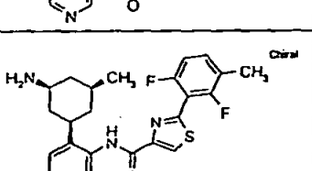
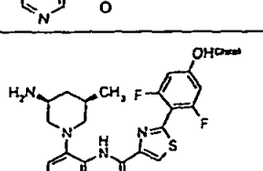
[0249] To a solution of (+/-)-2-(tert-butoxycarbonylamino)-4-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)-6-methylcyclohexyl acetate in MeOH (0.03 M) was added potassium carbonate (3.0 equiv.) and the reaction was stirred at room temperature for 3 h. Upon completion, the reaction was partititioned between water and ethyl acetate. The aqueous phase was further extracted 3 more times with ethyl acetate. The organics were combined, dried with brine and sodium sulfate, filtered, and concentrated. Isolated tert-butyl (+/-)-5-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)-2-hydroxy-3-methylcyclohexylcarbamate was obtained as an off-white solid in 87% yield. LC/MS = 545.2 (M+H), Rt = 0.75 min. To a solution of tert-butyl (+/-)-5-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)-2-hydroxy-3-methylcyclohexylcarbamate (1.0 equiv.) in DCM (0.07M) at 0 °C was added DAST (1.0 equiv.) under a nitrogen atmosphere. The reaction was stirred for 1 h, upon which time, 2 more equivalents of DAST were added. After 30 min, the consumption of the starting material was complete. The reaction was quenched by the addition of water, the organic phase was dried with sodium sulfate, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford tert-butyl (+/-)-5-(3-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyridin-4-yl)-2-fluoro-3-methylcyclohexylcarbamate as a clear oil in 60% yield. LC/MS = 547.3 (M+H), Rt = 0.92 min. The Boc group was removed by treating with 25% TFA in dichloromethane for 2 hours. Upon concentration under vacuo, the crude was purified via semi-prep HPLC. The pure fractions were lyophilized to yield N-

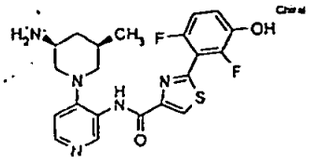
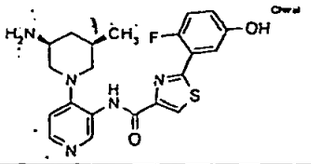
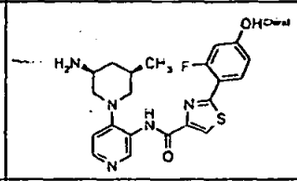
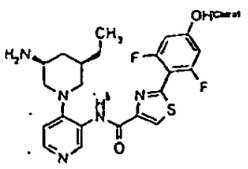
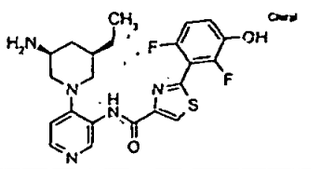
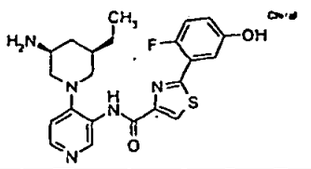
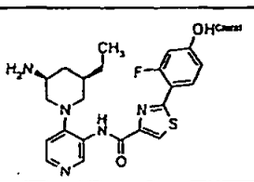
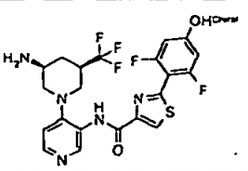
(4-((+/-)-3-amino-4-fluoro-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide as the desired product as the TFA salt in 74% yield. LC/MS = 447.0 (M+H), Rt = 0.56 min.

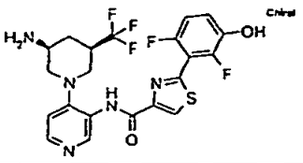
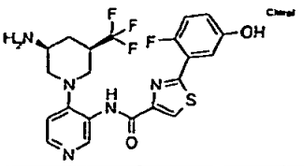
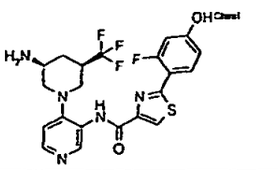
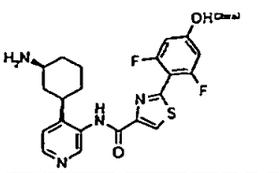
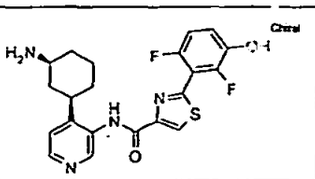
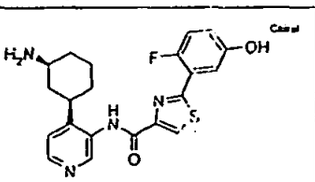
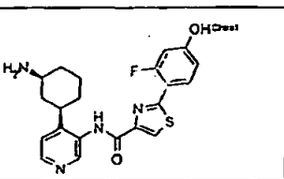
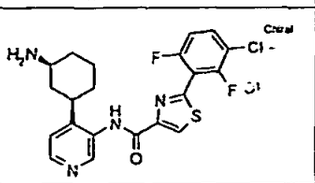
[0250] The following compounds are prepared using the techniques and procedures described herein.

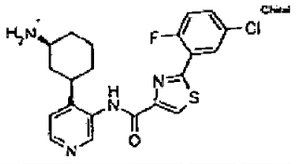
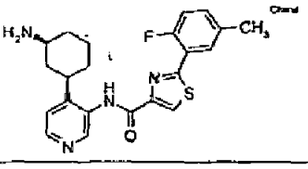
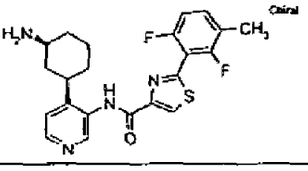
Example	Structure	Name
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60		2-(2-Fluoro-5-methyl-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
61		2-(2,3,6-Trifluoro-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
62		2-(2-Fluoro-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
63		2-(2-Chloro-6-fluoro-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
64		2-(2,6-Difluoro-3-methoxy-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide

Example	Structure	Name
65		2-Phenyl-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
66		2-(2-Chloro-phenyl)-thiazole-4-carboxylic acid (3-amino-4-hydroxy-5-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
67		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide
68		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide
69		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide
70		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
71		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
72		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide

Example	Structure	Name
73		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
74		2-(3-Chloro-2,6-difluoro-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
75		2-(5-Chloro-2-fluoro-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
76		2-(2-Fluoro-5-methyl-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
77		2-(2,6-Difluoro-3-methyl-phenyl)-thiazole-4-carboxylic acid [4-(5-amino-3,3-dimethyl-cyclohexyl)-pyridin-3-yl]-amide
78		2-(2-Fluoro-5-methyl-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide
79		2-(2,6-Difluoro-3-methyl-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-5-methyl-cyclohexyl)-pyridin-3-yl]-amide
80		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide

Example	Structure	Name
81		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
82		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
83		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-methyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
84		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-ethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
85		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-ethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
86		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-ethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
87		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-ethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
88		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide

Example	Structure	Name
89		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
90		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
91		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid (5-amino-3-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide
92		2-(2,6-Difluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
93		2-(2,6-Difluoro-3-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
94		2-(2-Fluoro-5-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
95		2-(2-Fluoro-4-hydroxy-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
96		2-(3-Chloro-2,6-difluoro-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide

Example	Structure	Name
97		2-(5-Chloro-2-fluoro-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
98		2-(2-Fluoro-5-methyl-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide
99		2-(2,6-Difluoro-3-methyl-phenyl)-thiazole-4-carboxylic acid [4-(3-amino-cyclohexyl)-pyridin-3-yl]-amide

Pim1 ATP depletion assay

[0251] 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 $MgCl_2$, and 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 the table 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*.

Pim2 ATP depletion assay

[0252] 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 $MgCl_2$, and 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 the table below.

Pim3 ATP depletion assay

[0253] 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 $MgCl_2$, and 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 the table below.

Cell Proliferation Assay

[0254] 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.

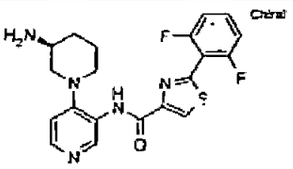
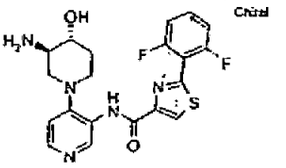
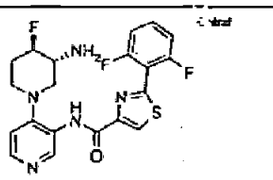
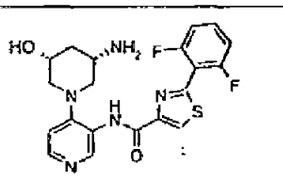
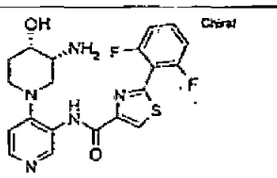
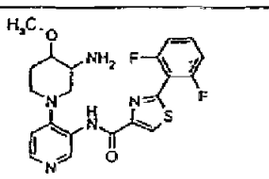
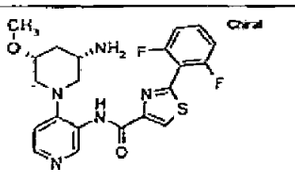
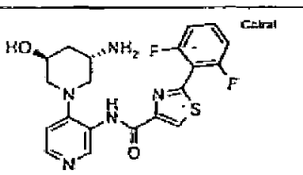
[0255] Test compounds supplied in DMSO were diluted into DMSO at 500 times the desired final concentrations before dilution into culture media to 2 times final concentrations. Equal volumes of 2x compounds were added to the cells in 96 well plates and incubated at 37 °C for 3 days.

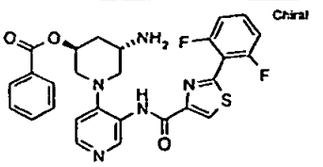
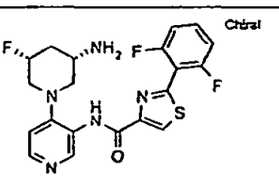
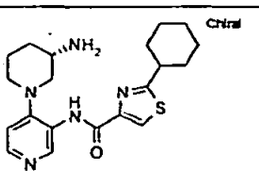
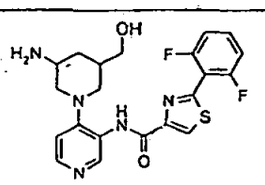
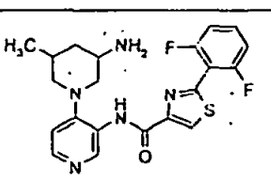
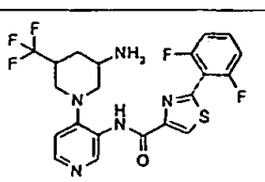
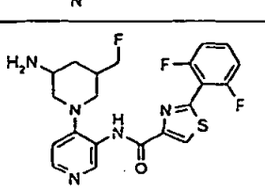
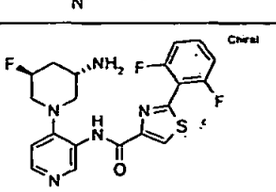
[0256] After 3 days plates were equilibrated to room temperature and equal volume of Cell Titer-Glow Reagent (Promega) was added to the culture wells. The plates were agitated briefly and luminescent signal was measured with luminometer. The percent inhibition of the signal seen in cells treated with 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 6 below.

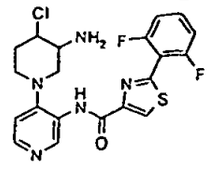
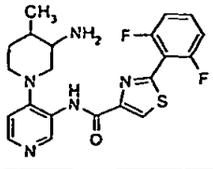
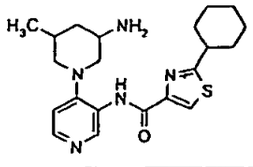
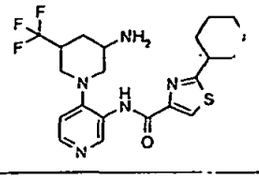
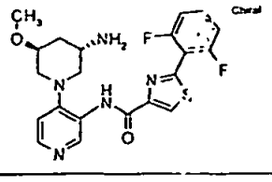
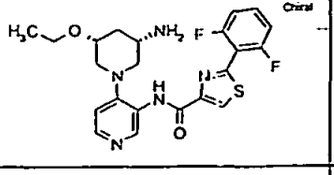
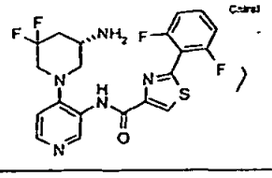
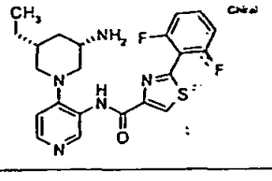
IC50 and EC50 Activity of Compounds of the Invention

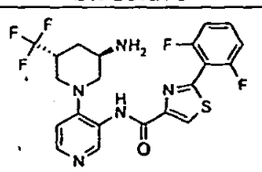
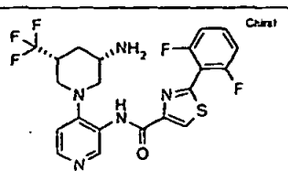
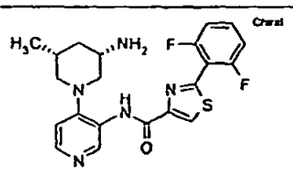
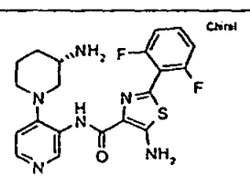
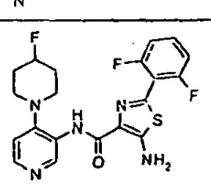
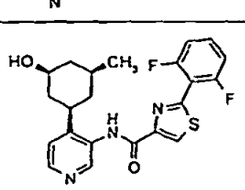
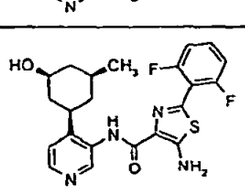
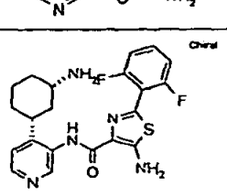
[0257] Using the procedures for Pim1 ATP depletion assay (PIM-1), Pim2 ATP depletion assay (PIM-2), and Pim3 ATP depletion assay (PIM-3), described above, the IC_{50} concentration of compounds of the previous examples were determined as shown in the following table.

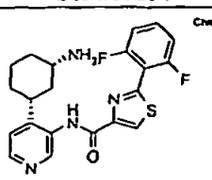
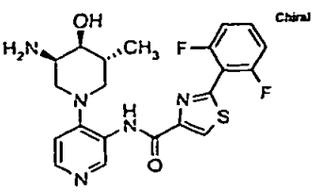
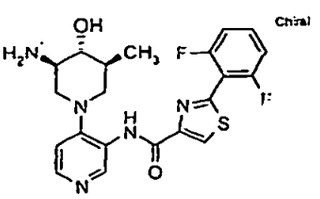
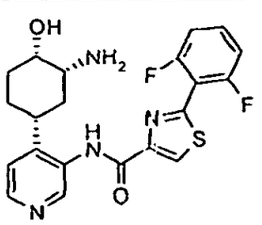
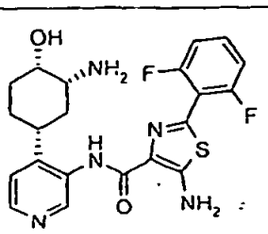
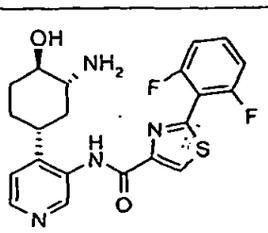
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)

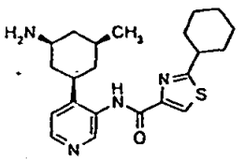
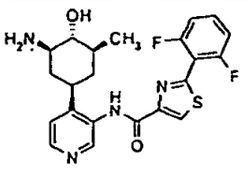
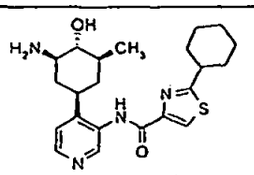
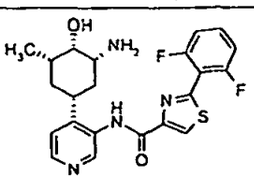
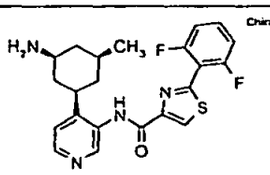
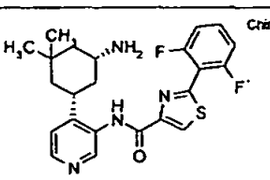
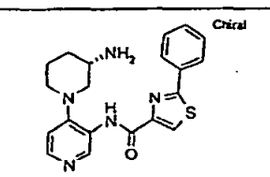
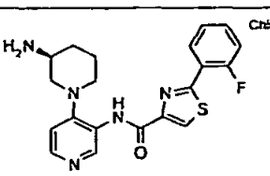
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
1		0.001	0.008	0.002
2		0.002	0.011	0.004
3		0.002	0.023	0.005
5		0.015	0.077	0.013
6		0.001	0.003	0.001
7		0.005	0.243	0.018
8		0.021	0.046	0.035
9		0.069	1.502	0.091

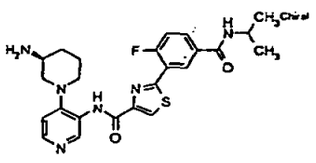
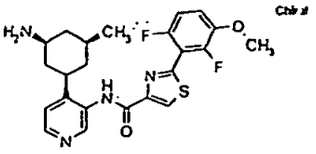
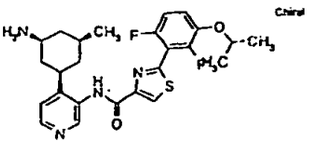
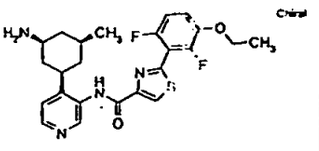
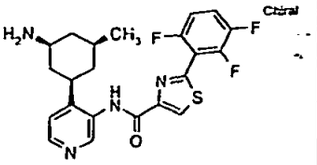
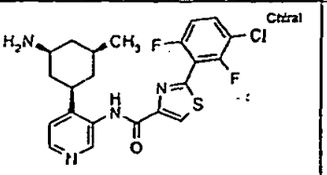
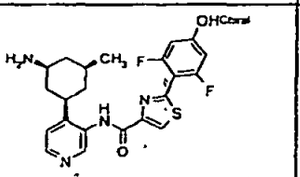
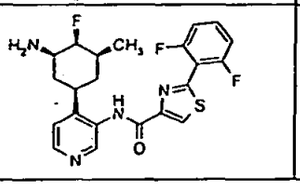
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
10		2.220	0.479	0.322
11		0.004	0.055	0.008
12		0.057	0.208	0.045
13		0.014	0.058	0.024
14		0.002	0.004	0.005
15		0.001	0.003	0.004
16		0.001	0.003	0.004
17		0.004	0.070	0.008

Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
18		0.005	0.054	0.012
19		0.001	0.008	0.005
20		0.012	0.018	0.016
21		0.011	0.021	0.020
22		0.129	0.378	0.060
23		0.056	0.085	0.086
24		0.002	0.038	0.004
25		0.001	0.003	0.003

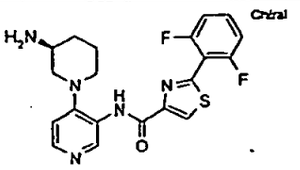
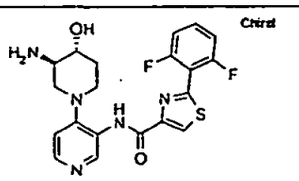
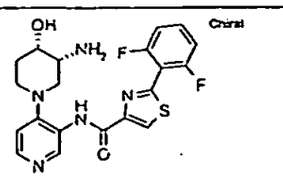
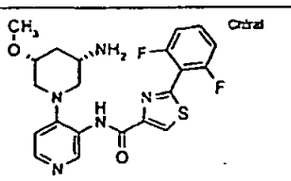
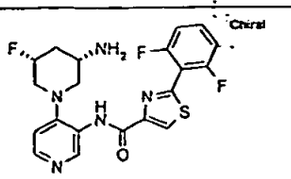
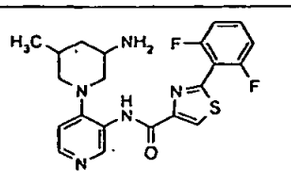
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
26		0.006	0.072	0.024
27		0.001	0.003	0.003
28		0.001	0.002	0.002
29		0.001	0.002	0.002
30		0.001	0.055	0.003
31		0.002	0.090	0.008
32		0.001	0.005	0.004
33		0.001	0.003	0.003

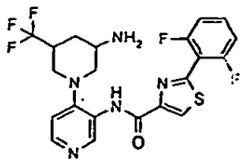
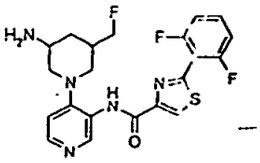
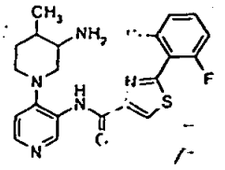
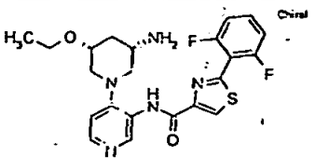
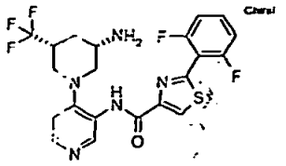
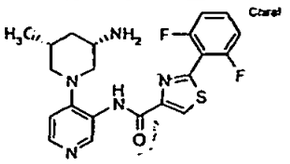
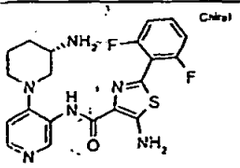
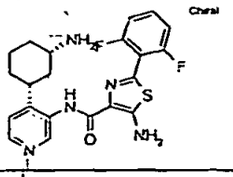
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
34		0.002	0.029	0.004
35		0.009	0.125	0.009
36		0.001	0.003	0.003
37		0.006	0.098	0.011
38		0.001	0.004	0.003
39		0.011	0.095	0.012

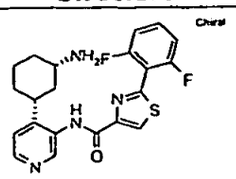
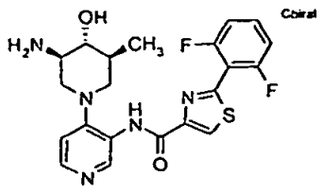
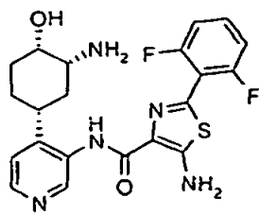
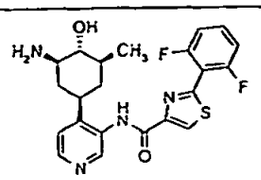
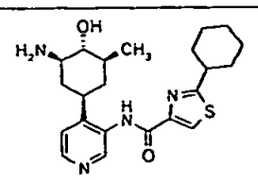
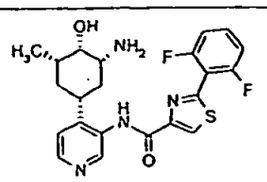
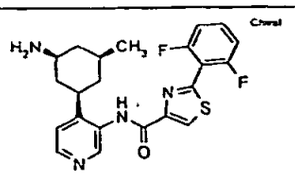
Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
40		0.041	0.097	0.109
41		0.004	0.027	0.008
42		0.146	0.250	0.215
43		0.005	0.046	0.015
45		0.001	0.007	0.003
46		0.001	0.016	0.003
48		0.0020	0.0177	0.0023
49		0.0019	0.0099	0.0042

Ex. No.	Structure	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
50		0.0032	0.0838	0.0083
52		0.001	0.004	0.002
53		0.001	0.020	0.003
54		0.001	0.009	0.003
55		0.003	0.015	0.005
56		0.001	0.012	0.003
57		0.001	0.004	0.002
58		0.004	0.047	0.018

[0258] Using the procedures for Cell Proliferation Assay described above, the EC_{50} concentration of compounds of the previous examples were determined in KMS11 cells as shown in the following table.

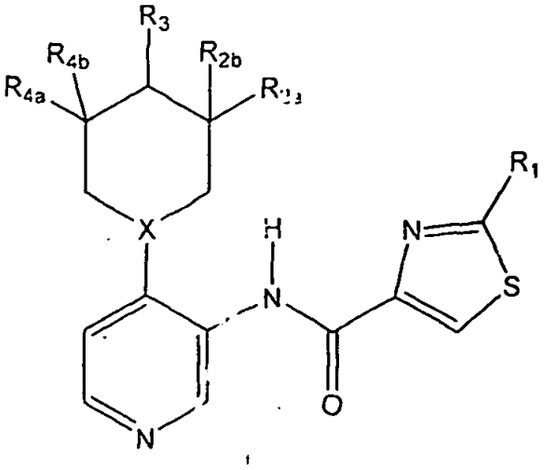
Ex. No.	Structure	KMS11 EC_{50} (μM)
1		1.17
2		1.57
6		0.41
8		4.70
11		6.10
14		0.83

Ex. No.	Structure	KMS11 EC_{50} (μM)
15		0.31
16		2.38
19		0.93
23		6.54
27		0.46
28		0.40
29		0.04
33		0.43

Ex. No.	Structure	KMS11 EC_{50} (μM)
34		5.02
36		0.56
38		1.89
41		>10
42		
43		
45		0.92

CLAIMS

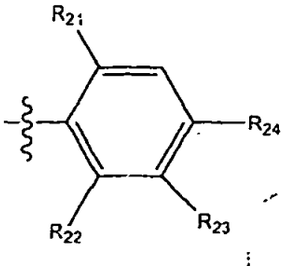
1. A compound of Formula I, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,

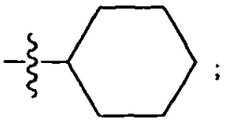


(I)

wherein,

R_1 is selected from



, and  ;

X represents CH, or N;

R_{2a} is selected from amino, methyl, CH_2F, CF_3, C_2H_5, and H;

R_{2b} is selected from H, and methyl;

R_3 is selected from H, OH, OCH_3, CH_3, F, and Cl;

R_{4a} is selected from amino, methyl, OH, OCH_3, OC_2H_5, F, CF_3, H, and ethyl;

R_{4b} is selected from methyl, H, and F;

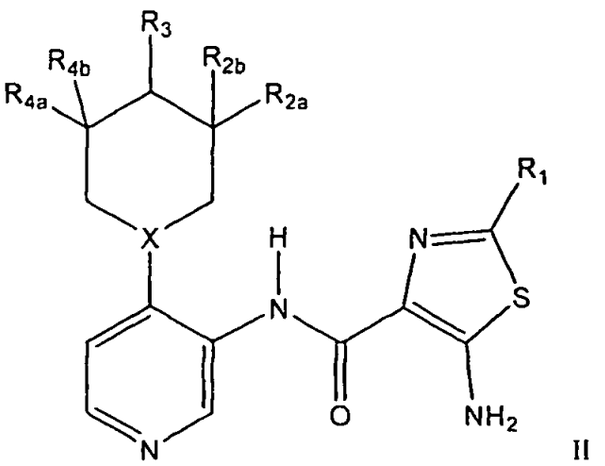
R_{21} represents H or F;

R_{22} represents H, Cl, or F;

R_{23} represents F, OC_2H_5, OCH_3, Cl, H, methyl, OH, or $OCH(CH_3)_2$; and

R_{24} represents H or OH.

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



II

wherein:

R_1 is selected from -NH-CO-alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

X represents CH or N;

R_{2a} is selected from -H, -OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo, amino and bezoate;

R_{2b} is selected from –H and alkyl;

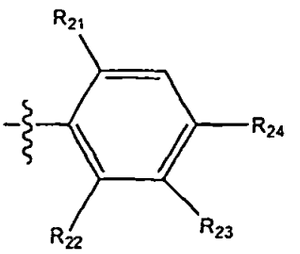
R_3 is selected from H, OH, alkyl, alkoxy and halo;

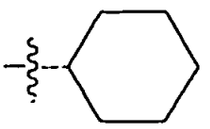
R_{4a} is selected from –OH, alkyl, alkoxy, haloalkyl, aminoalkyl, hydroxyalkyl, halo and amino; and

R_{4b} is selected from H, alkyl and halo.

3. A compound of Claim 2 wherein R_1 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, and substituted or unsubstituted piperidinyl.

4. A compound of Claim 3 wherein R_1 is selected from



, and  ;

wherein:

R_{21} is H or halo;

R_{22} is H or halo;

R_{23} is selected from H, halo, alkyl and alkoxy; and

R_{24} is H or OH;

5. A compound of Claim 4 wherein R_{21} and R_{22} are independently selected from H or F.

6. A compound of Claim 4 wherein R_{23} is selected from H, Cl, F, $-OC_2H_5$, $-OCH_3$, and $-OCH(CH_3)_2$.

7. A compound of Claim 2 wherein R_2 is selected from H, methyl, ethyl, methoxy, ethoxy, fluoromethyl, trifluoromethyl, aminomethyl and hydroxymethyl.

8. A compound of Claim 2 wherein R_3 is selected from H, -OH, methyl, methoxy, F and Cl.

9. A compound of Claim 2 wherein R_{4a} is selected from -OH, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, amino, F and Cl.

10. A compound of Claim 2 wherein R_{4b} is selected from methyl and F.

11. A compound of Claim 1 or Claim 2 selected from the group consisting of (S)-5-amino-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)-thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-

methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-ethylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-4-hydroxyphenyl)thiazole-4-carboxamide, 5-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-5-(fluoromethyl)piperidin-1-yl)-pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide, 5-amino-2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-4-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(3-ethoxy-2,6-difluorophenyl)-thiazole-4-carboxamide, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

12. A compound of Claim 1 or 2 selected from the group consisting of (S)-5-amino-N-(4-(3-aminopiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, 5-amino-N-(4-((1R,3S)-3-aminocyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((3S,5R)-3-amino-5-ethylpiperidin-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-4-hydroxyphenyl)thiazole-4-carboxamide, 5-amino-N-(4-(3-amino-4-hydroxycyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-(3-amino-5-(fluoromethyl)piperidin-1-yl)-pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carbox-

amide, 5-amino-2-(2,6-difluorophenyl)-N-(4-((1R,3S,5S)-3-hydroxy-5-methylcyclohexyl)pyridin-3-yl)thiazole-4-carboxamide, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

13. 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 any one of Claims 1 through Claim 12.

14. A composition comprising a therapeutically effective amount of compound of any one of Claims 1 through Claim 12, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

15. A method for inhibiting PIM kinase activity in a cell, comprising contacting the cell with an effective amount of a compound of any one of Claims 1 through Claim 12.

15. 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 any one of Claims 1 through Claim 12.

16. A method for inhibiting PIM kinase activity in a patient, comprising administering to the patient a composition comprising a pharmacologically effective amount of a compound of any one of Claims 1 through Claim 12.

17. A method for treating a cancer disorder in a patient, comprising administering to the patient a composition comprising an amount of a compound of any one of Claims 1 through Claim 12 effective to inhibit PIM kinase activity in the patient.

18. A compound of any one of Claims 1 through Claim 12 for use as a therapeutic agent.

19. A compound of any one of Claims 1 through Claim 12 for use in manufacture of a medicament for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/052506

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 C07D417/14 A61K31/4439 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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 2 649 043 A1 (ASTELLAS PHARMA INC [JP]) 1 November 2007 (2007-11-01) claims 1,9	1-12
A	WO 2007/058942 A (SCHERING CORP [US]; ZHAO LIANYUN [US]; CURRAN PATRICK J [US]; BELANGER) 24 May 2007 (2007-05-24) claims 59,60,62,63	1-19
X,P	WO 2008/054701 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08) claim 1	1-19
X,P	WO 2008/054702 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08) claims 1,43,48	1-19

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

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2009	11/05/2009

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	Brandstetter, T

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/052506

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2008/054749 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08) claims 1,48,53	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/052506

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CA 2649043 A1	01-11-2007	EP 2009005 A1	31-12-2008
		WO 2007123269 A1	01-11-2007
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		EC SP083440 A	30-06-2008
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		KR 20080074963 A	13-08-2008
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WO 2008054749 A	08-05-2008	AR 063531 A1	28-01-2009
		CL 3382007 A1	27-06-2008

TCP **OMPI**

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SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)

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(51) Clasificación de Patentes Internacional[7]:
C07D 417/12 (2006.01) *A61K 31/4439* (2006.01)
C07D 417/14 (2006.01) *A61P 35/00* (2006.01)

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(74) Agente: **VON SPRECHER, Georg**; (CH) NOVARTIS PHARMA AG, Patent Department, 4002 Basel (CH).

(81) Estados designados (a menos que se indique de otra manera, para cada clase de protección nacional disponible): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

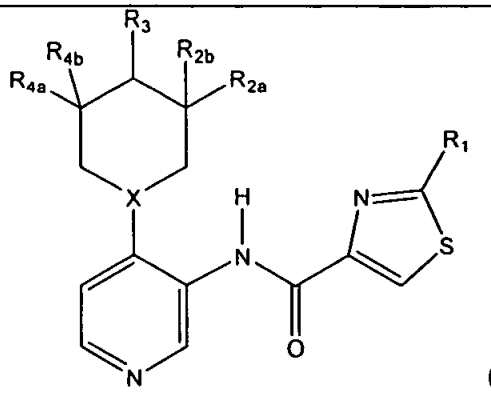
(82) Estados designados (a menos que se indique de otra manera, para cada clase de protección regional disponible): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la Regla 4.17:
- en cuanto al derecho del solicitante para solicitar y ser otorgado una patente (Regla 4.17(ii))

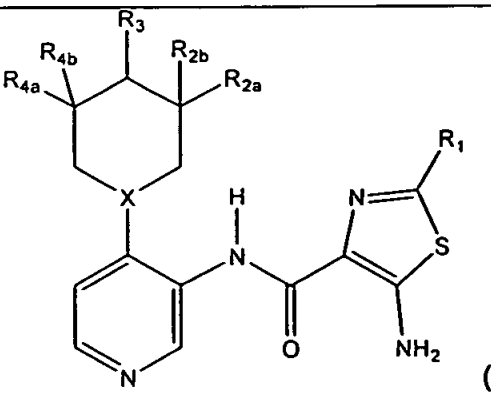
Publicada:
Con reporte de búsqueda internacional (Art. 21(3))

(54) Título: **INHIBIDORES DE CINASA PIM Y MÉTODOS PARA SU USO**

(57) Resumen: La presente invención se refiere a nuevos compuestos de las fórmulas I y II, a sus tautómeros, estereoisómeros y polimorfos, 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 inhibición de la actividad de la cinasa Pim y/o en la profilaxis o el tratamiento de cáncer.



(I)



(II)

INHIBIDORES DE CINASA PIM Y MÉTODOS PARA SU USO

Campo de la invención

La presente invención se refiere a nuevos compuestos, a sus tautómeros, estereoisómeros y polimorfos, 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 a los usos 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 los 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 HT y colaboradores, "Murine leukemia virus-induced T-cell lymphomagenesis: 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 lymphomas" *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 lymphoma 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 hematopoyéticas. 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 hematopoyéticas (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 leukemia 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", *Leukemia* **20**: 1774–1782 (2006)) y en el cáncer de próstata (Dhanasekaran SM, y colaboradores, "Delineation of prognostic biomarkers in prostate cancer", *Nature* 412(6849): 822-6 (2001); Cibull TL, y colaboradores, "Overexpression of Pim-1 during progression 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 en el 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 hematopoyéticas 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 Ser112 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", *Biochim 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

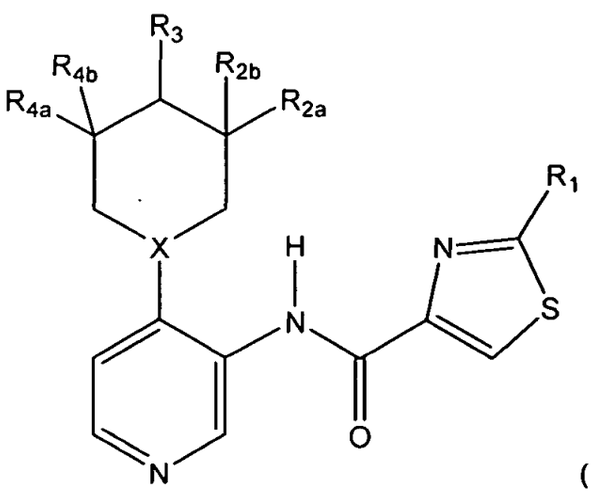
Pim(s) con el siARN, da como resultado la inhibición de la proliferación y muerte celular (Dai JM, y colaboradores, "Antisense oligodeoxynucleotides targeting the serine / threonine kinase Pim-2 inhibited proliferation of DU-145 cells", *Acta Pharmacol Sin* **26(3)**: 364-8 (2005); Fujii y colaboradores 2005; Li y colaboradores 2006). Adicionalmente, se piensa que la activación mutacional de varios oncogenes bien conocidos en las malignidades hematopoyéticas 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 hematopoyéticas 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 descripción de la invención

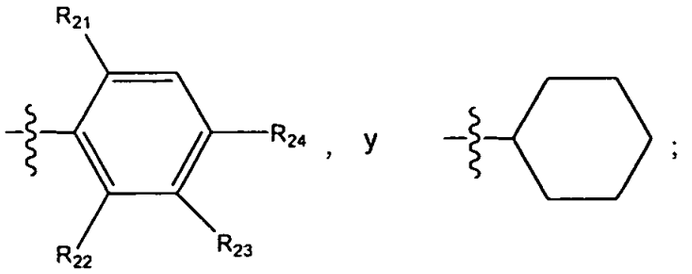
La presente invención proporciona un compuesto de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



(I)

en donde:

R_1 se selecciona a partir de:



X representa CH o N;

R_{2a} se selecciona a partir de amino, metilo, CH_2F, CF_3, C_2H_5, y H;

R_{2b} se selecciona a partir de H, y metilo;

R_3 se selecciona a partir de H, OH, OCH_3, CH_3, F, y Cl;

R_{4a} se selecciona a partir de amino, metilo, OH, OCH_3, OC_2H_5, F, CF_3, H, y etilo;

R_{4b} se selecciona a partir de metilo, H, y F;

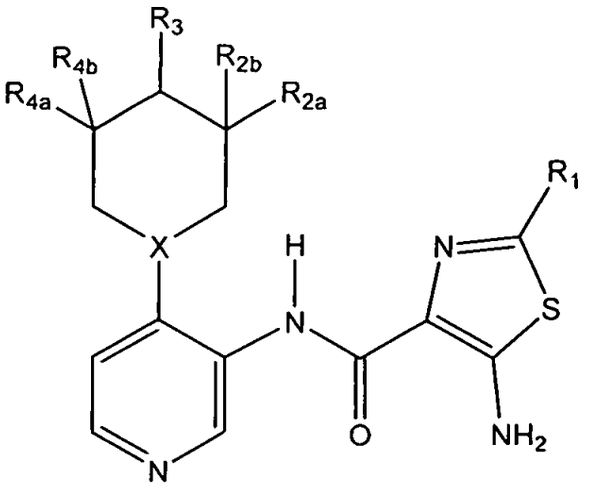
R_{21} representa H o F;

R_{22} representa H, Cl, o F;

R_{23} representa F, OC_2H_5, OCH_3, Cl, H, metilo, OH, u $OCH(CH_3)_2$; y

R_{24} representa H u OH.

En otro aspecto, la presente invención proporciona un compuesto de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



II

en donde:

R_1 se selecciona a partir de -NH-CO-alquilo, cicloalquilo sustituido o insustituido, hetero-cicloalquilo sustituido o insustituido, arilo sustituido o insustituido, y hetero-arilo sustituido o insustituido;

X representa CH o N;

R_{2a} se selecciona a partir de -H, -OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno, amino y benzoato;

R_{2b} se selecciona a partir de –H y alquilo;

R_3 se selecciona a partir de H, OH, alquilo, alcoxilo y halógeno;

R_{4a} se selecciona a partir de –OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno y amino; y

R_{4b} se selecciona a partir de H, alquilo y halógeno.

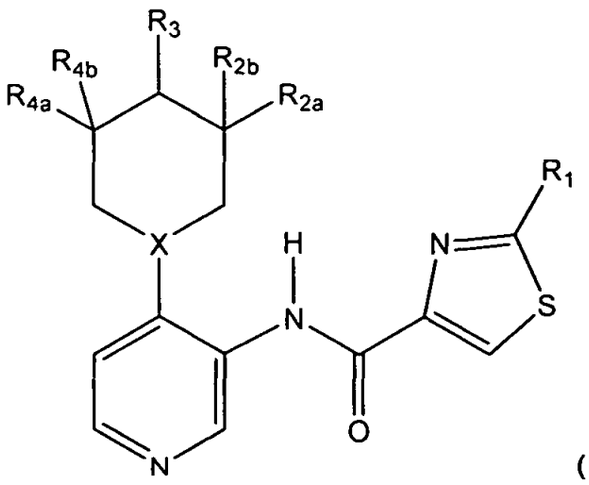
Otro aspecto de la presente invención proporciona una composición que comprende una cantidad terapéuticamente efectiva del compuesto de la fórmula I o de la fórmula II, o un

estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, junto con un vehículo farmacéuticamente aceptable.

En otro aspecto de la presente invención, se proporciona un método para inhibir la actividad de la cinasa PIM en una célula, el cual comprende poner en contacto la célula con una cantidad efectiva de un compuesto de la fórmula I o de la fórmula II. Todavía otro aspecto 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 (PIM cinasa), el cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula I o de la fórmula II.

Descripción detallada de la invención

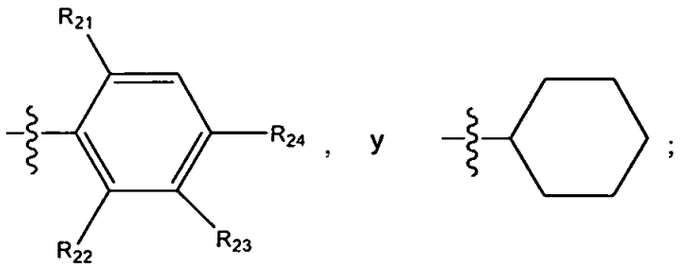
En un aspecto, la presente invención proporciona los compuestos de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos,



(I)

en donde:

R_1 se selecciona a partir de:



, y ;

X representa CH o N;

R_{2a} se selecciona a partir de amino, metilo, CH_2F, CF_3, C_2H_5, y H;

R_{2b} se selecciona a partir de H, y metilo;

R_3 se selecciona a partir de H, OH, OCH_3, CH_3, F, y Cl;

R_{4a} se selecciona a partir de amino, metilo, OH, OCH_3, OC_2H_5, F, CF_3, H, y etilo;

R_{4b} se selecciona a partir de metilo, H, y F;

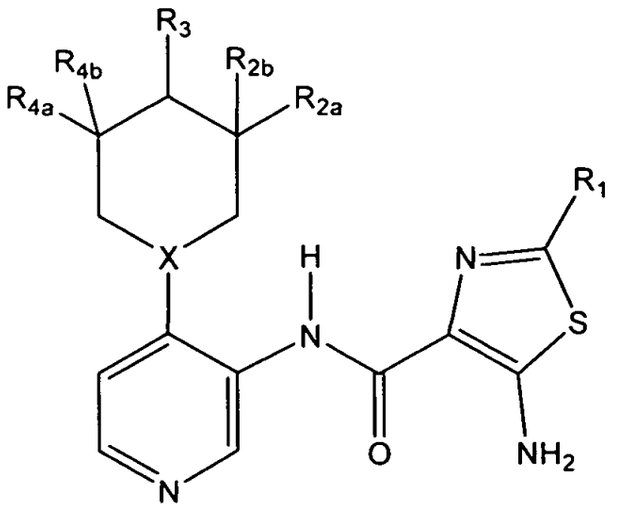
R_{21} representa H o F;

R_{22} representa H, Cl, o F;

R_{23} representa F, OC_2H_5, OCH_3, Cl, H, metilo, OH, u $OCH(CH_3)_2$; y

R_{24} representa H u OH.

En otro aspecto, la presente invención proporciona un compuesto de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo,



II

en donde:

R1 se selecciona a partir de -NH-CO-alquilo, cicloalquilo sustituido o insustituido, hetero-cicloalquilo sustituido o insustituido, arilo sustituido o insustituido, y hetero-arilo sustituido o insustituido;

X representa CH o N;

R_{2a} se selecciona a partir de -H, -OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno, amino y benzoato;

R_{2b} se selecciona a partir de –H y alquilo;

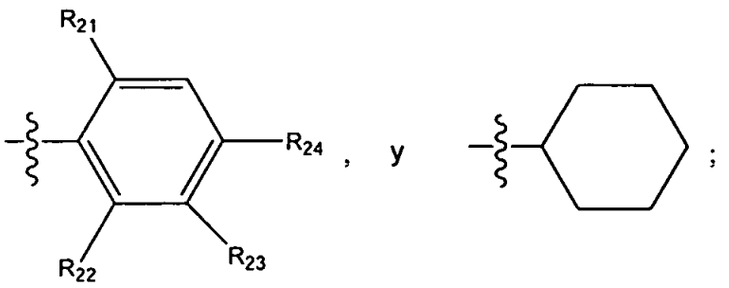
R_3 se selecciona a partir de H, OH, alquilo, alcoxilo y halógeno;

R_{4a} se selecciona a partir de –OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno y amino; y

R_{4b} se selecciona a partir de H, alquilo y halógeno.

En algunos aspectos, la invención proporciona los compuestos de la fórmula II en donde R_1 se selecciona a partir de fenilo sustituido o insustituido, ciclohexilo sustituido o insustituido, y

piperidinilo sustituido o insustituido. En otros aspectos, la invención proporciona los compuestos de la fórmula II en donde R_1 se selecciona a partir de:



, y ;

en donde:

R_{21} es H o halógeno;

R_{22} es H o halógeno;

R_{23} se selecciona a partir de H, halógeno, alquilo y alcoxilo; y

R_{24} es H o OH.

En algunas modalidades de la invención, R_{21} y R_{22} se seleccionan independientemente a partir de H o F. En otras modalidades, R_{23} se selecciona a partir de H, Cl, F, $-OC_2H_5$, $-OCH_3$, y $-OCH(CH_3)_2$.

En otras modalidades, la invención proporciona los compuestos de la fórmula II en donde R_2 se selecciona a partir de H, metilo, etilo, metoxilo, etoxilo, fluoro-metilo, trifluoro-metilo, amino-metilo e hidroxi-metilo.

Todavía otras modalidades proporcionan los compuestos de la fórmula II en donde R_3 se selecciona a partir de H, -OH, metilo, metoxilo, F y Cl.

En algunas modalidades, la invención proporciona los compuestos de la fórmula II en donde R_{4a} se selecciona a partir de -OH, metilo, etilo, trifluoro-metilo, metoxilo, etoxilo, amino, F y Cl. Otras modalidades proporcionan los compuestos de la fórmula II en donde R_{4b} se selecciona a partir de metilo y F.

En algunas modalidades actualmente preferidas, la invención proporciona un compuesto de la fórmula I o de la fórmula II seleccionado a partir del grupo que consiste en (S)-5-amino-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-etil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-(3-amino-5-(fluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida, 5-amino-2-(2,6-difluoro-fenil)-N-(4-((1R,3S, 5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida, N-

(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-(3-amino-4-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(3-etoxi-2,6-difluoro-fenil)-tiazol-4-carboxamida, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de las mismas.

En otras modalidades actualmente preferidas, la invención proporciona un compuesto de la fórmula I o de la fórmula II seleccionado a partir del grupo que consiste en (S)-5-amino-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-etil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-(3-amino-5-(fluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida, 5-amino-2-(2,6-difluoro-fenil)-N-(4-((1R,3S,

5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de las mismas.

Otro aspecto de la presente invención proporciona una composición que comprende una cantidad terapéuticamente efectiva del compuesto de la fórmula I o de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, junto con un vehículo farmacéuticamente aceptable.

En otro aspecto de la presente invención, se proporciona un método para inhibir la actividad de la cinasa PIM en una célula, el cual comprende poner en contacto la célula con una cantidad efectiva de un compuesto de la fórmula I o de la fórmula II. Todavía otro aspecto 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 (PIM cinasa), el cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un compuesto de la fórmula I o de la fórmula II.

Una modalidad preferida de este aspecto de la presente invención proporciona un método para el tratamiento de un trastorno de cáncer en un paciente, el cual comprende administrar al paciente una composición que comprende una cantidad de un compuesto de la reivindicación 1 o de la reivindicación 10, efectiva para inhibir la actividad de la cinasa PIM en el paciente.

Otro aspecto de la presente invención proporciona un compuesto de cualquiera de la fórmula I o de la fórmula II, para utilizarse como un agente terapéutico. Todavía otro aspecto de la presente invención proporciona el uso de cualquiera de los compuestos de la fórmula I o de la fórmula II, en la fabricación de un medicamento para el tratamiento de cáncer.

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 grupos alquilo que no contienen heteroátomos. 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.

Como se utiliza en la presente, el término "halógeno" o "halo" se refiere a 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 inferior" se refiere a un radical de alquilo inferior sustituido con uno o más átomos de halógeno. El término "halo-alcoxilo" se refiere a un radical de alcoxilo sustituido con uno o más átomos de halógeno. El término "halo-alcoxilo inferior" se refiere a un radical de alcoxilo inferior sustituido con uno

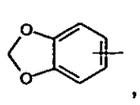
o más átomos de halógeno.

"Amino" se refiere en la presente al grupo $-NH_2$, el cual puede estar sustituido para formar -NRR'. 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 "alcoxilo" se refiere a RO- en donde R es alquilo sustituido o insustituido. Los ejemplos representativos de los grupos alcoxilo inferior incluyen metoxilo, etoxilo, terbutoxilo, trifluoro-metoxilo y similares.

"Cicloalquilo" se refiere a un sustituyente de alquilo mono- o poli-cíclico, heterocíclico o carbocíclico. 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 heteroátomo. El término "hetero-cicloalquilo" o "heterociclilo" se refiere en la presente a los sustituyentes de cicloalquilo que tienen de 1 a 5, y más típicamente de 1 a 4 heteroátomos en la estructura del anillo. Los heteroátomos 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.

"Arilo" se refiere a grupos aromáticos monocíclicos y policíclicos opcionalmente sustituidos que tienen de 3 a 14 átomos de carbono o heteroátomos 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 heteroátomos 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,

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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.

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, incluyendo los compuestos de las fórmulas (I) o (II) 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, incluyendo los compuestos de las fórmulas (I) o (II) 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 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 las fórmulas (I) o (II). Estas sales se pueden preparar *in situ* durante el aislamiento y purificación final de los compuestos de las fórmulas (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, alcanforato, alcanfor-sulfonato, digluconato, ciclopentan-propionato, dodecil-sulfato, etan-

sulfonato, glucoheptanoato, glicerofosfato, hemisulfato, 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 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 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 del ácido farmacéuticamente aceptables incluyen los ácidos inorgánicos como ácido clorhídrico, ácido sulfúrico y ácido fosfórico, y los ácidos orgánicos 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 metales alcalinos y alcalinotérreos, tales como sales de sodio, litio, potasio, calcio, magnesio, aluminio, y similares, así como los cationes no tóxicos de amonio, de amonio cuaternario, y de 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 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.

Será evidente para los expertos en este campo que los compuestos de la invención, incluyendo los compuestos de las fórmulas (I) o (II) 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 técnicas de rutina conocidas en este campo. 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 las fórmulas (I) o (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.

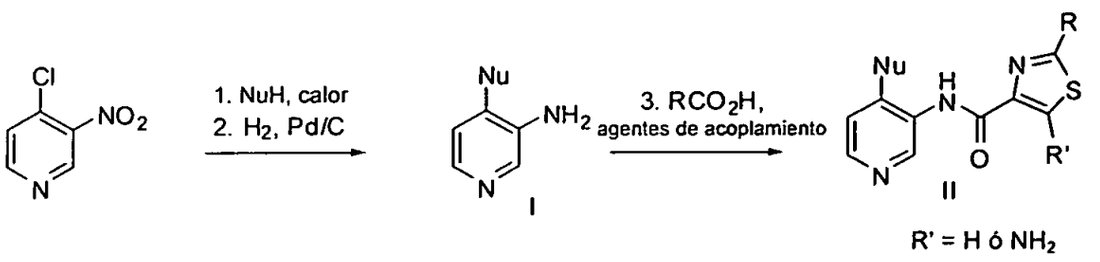
El término "cáncer" se refiere las enfermedades de cáncer que se pueden tratar benéficamente mediante la inhibición de la cinasa Pim, incluyendo, por ejemplo, cánceres sólidos, tales como carcinomas (por ejemplo, de los pulmones, páncreas, tiroides, ovarios, vejiga, mama, próstata, o colon), melanomas, trastornos mieloides (por ejemplo, leucemia mieloide, mieloma múltiple, y eritroleucemia), adenomas (por ejemplo, adenoma villoso de colon),

y sarcomas (por ejemplo, osteosarcoma).

Métodos Sintéticos

Los compuestos de la invención se pueden obtener a través de procedimientos conocidos por el experto en la materia. Por ejemplo, como se muestra en el Esquema 1, la 4-cloro-3-nitro-piridina se puede hacer reaccionar con un nucleófilo, proporcionando, después de la reducción de nitro, una 3-amino-piridina 4-sustituida I. Las amino-piridinas sustituidas I se pueden acilar con ácidos tiazol-carboxílicos, con la ayuda de agentes de acoplamiento, o con los haluros de ácido o los anhídridos de ácido, proporcionando las piridinas 3,4-disustituidas II. Si el grupo R en la posición 2 del tiazol es bromo, triflato o yodo, se puede llevar a cabo una modificación adicional para incorporar una variedad de sustituyentes en esta posición, mediante reacciones de formación de enlace de carbono-carbono mediadas por metal.

Esquema 1

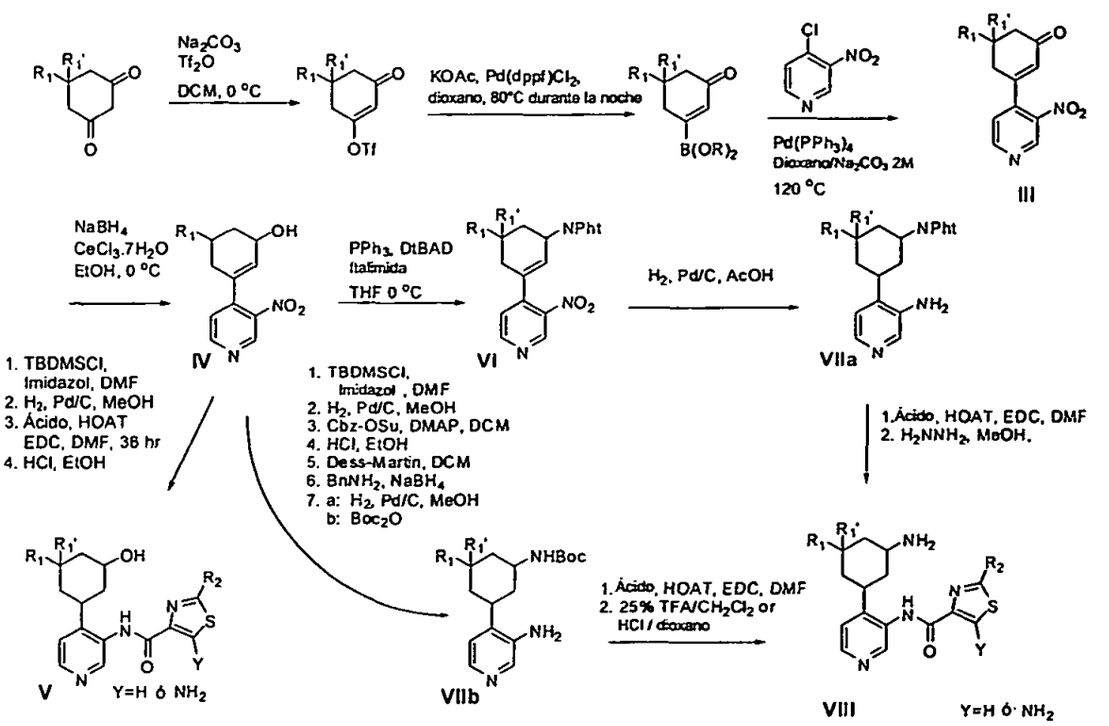


La reacción de la 4-cloro-3-nitro-piridina con nucleófilos, como se ilustra en el Esquema 1, no está limitada a los nucleófilos

basados en nitrógeno; también se pueden formar enlaces de carbono-carbono con la adición neta de nucleófilos de carbono. Como se muestra en el Esquema 2, las ciclohexanodionas se pueden convertir por medio de monotriflatos hasta los ésteres de ciclohexenona-boronato correspondientes, los cuales pueden someterse a formación de enlace de carbono-carbono mediada por paladio con la 4-cloro-3-nitro-piridina, para proporcionar las ciclohexenonas sustituidas por nitro-piridina III. La reducción de la funcionalidad de enona puede proporcionar un ciclohexenol IV que, después de la protección de alcohol, la reducción de nitro y alqueno, el acoplamiento de amida y la desprotección, puede proporcionar las ciclohexanol-amidas V. El ciclohexenol IV también puede someterse a reacción de Mitsunobo con ftalimida para proporcionar un amino-ciclohexeno protegido V. En seguida de la reducción de nitro y alqueno, la amino-ciclohexil-piridil-anilina protegida por ftalimida VIIa puede someterse a acoplamiento de amida y desprotección, para proporcionar las amino-ciclohexan-amidas VIII. La amino-ciclohexan-piridil-anilina protegida por Boc VIIb correspondiente también se puede preparar a partir del ciclohexenol IV 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 bencilo, y protección con Boc de amina alifática primaria. En los productos de amida V y VIII, si R_2 es halógeno o triflato, las amidas IV y VIII se pueden modificar

adicionalmente mediante modificaciones convencionales para introducir arilos, alquilos, y heteroarilos sustituidos en R_2. Por ejemplo, si R_2 es Br, mediante la reacción con ácidos borónicos o con reactivos organometálicos, o mediante la conversión hasta el éster de boronato correspondiente y la reacción con haluros de arilo/heteroarilo o triflatos, son posibles una variedad de modificaciones de R_2.

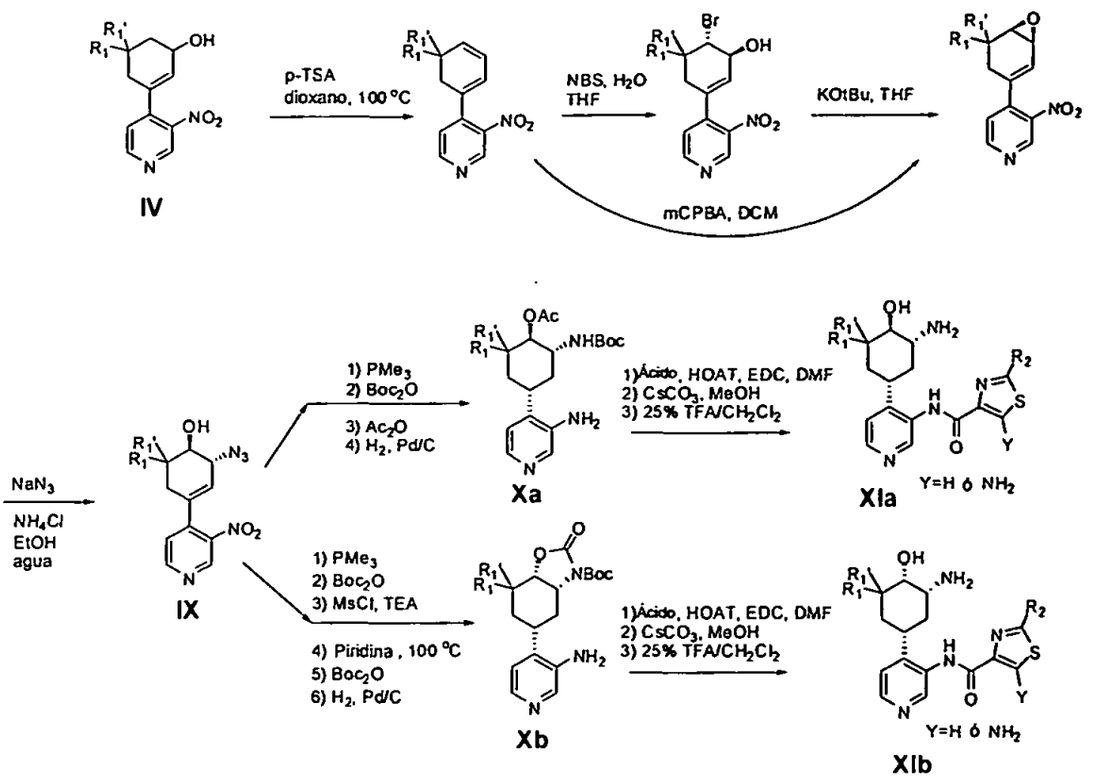
Esquema 2



Las tiazol-amidas con grupos ciclohexilo sustituidos se pueden obtener mediante la modificación del nitro-piridil-ciclohexenol IV.

Como se muestra en el Esquema 3, el ciclohexenol IV se puede deshidratar proporcionando un ciclohexadieno que, después de la epoxidación (mediante la formación de bromo-hidrina y la eliminación de HBr, o a partir de mCPBA directamente) y de la abertura del epóxido de azida, proporciona el ciclohexenil-azido-alcohol IX. El ciclohexenil-azido-alcohol IX se puede convertir hasta la amino-hidroxi-anilina trans-protegida Xa mediante reducción de azida, protección de alcohol, y reducción de alqueno y nitro. De una manera alternativa, el ciclohexenil-azido-alcohol IX se puede convertir hasta la amino-hidroxi-anilina cis-protegida Xb mediante reducción de azida y protección de Boc, mesilación de alcohol y ciclación intramolecular hasta el carbamato cis cíclico, seguida por protección de Boc y reducción de alqueno y nitro. Las ciclohexil-piridil-anilinas Xa y Xb resultantes se pueden convertir hasta las tiazol-amidas XIa y XIb correspondientes mediante acoplamiento de amida, disociación de acetato o de carbamato cíclico, y desprotección de Boc. Si R_2 es halógeno o triflato, las amidas XIa y XIb y XII se pueden modificar adicionalmente mediante modificaciones convencionales para introducir 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 con reactivos organometálicos, o mediante la conversión hasta el éster de boronato correspondiente y la reacción con haluros de arilo/heteroarilo o triflatos, son posibles una variedad de modificaciones de R_2.

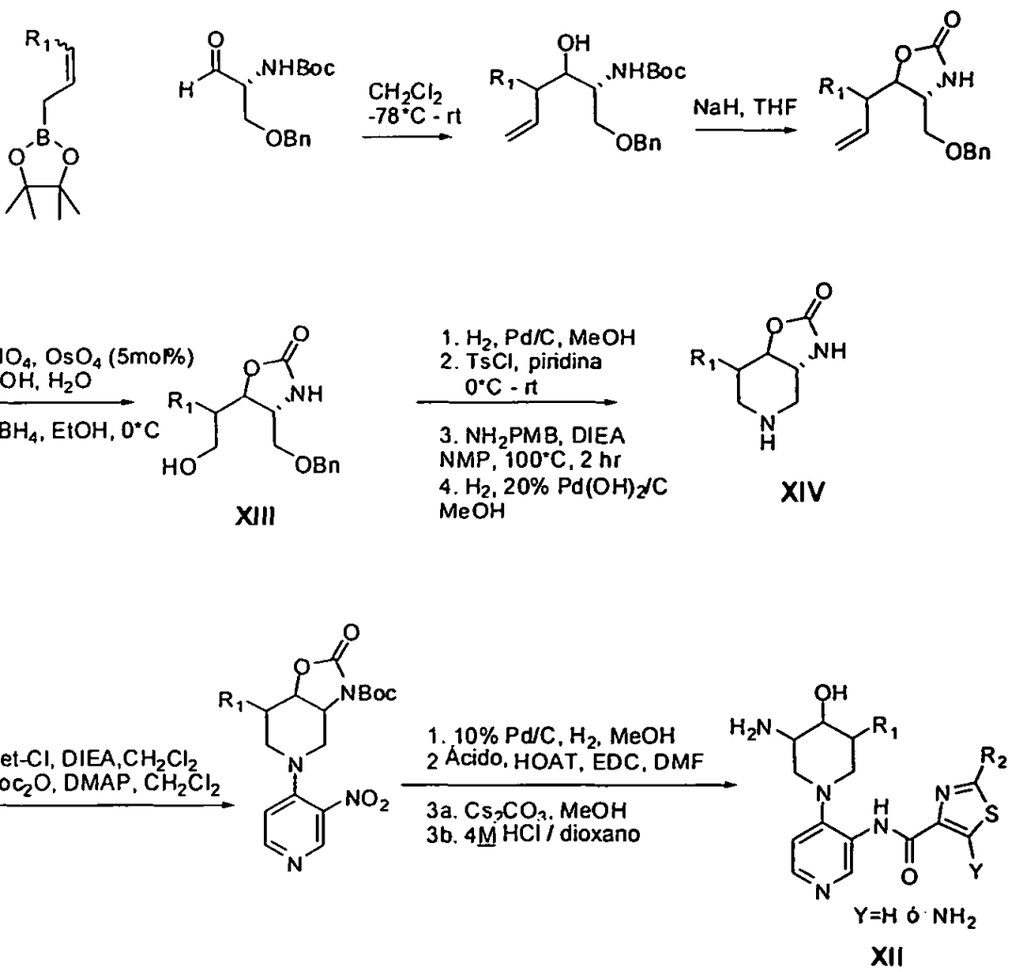
Esquema 3



Las 3-amino-piperidinas sustituidas se pueden preparar y modificar para proporcionar las 3-amino-piperidinil-tiazol-amidas sustituidas XII como se ilustra en el Esquema 4. La reacción de los ésteres de boronato de crotilo con SerOBn-aldehído, seguida por la formación de carbamato cíclico, la disociación oxidativa de alqueno, y la reducción, proporcionan el compuesto de hidroxilo XIII. La desprotección de bencilo, seguida por bis-tosilación, y la reacción con p-metoxi-bencil-amina, y la desprotección de amina, proporcionan la piperidina XIV. mediante el uso de ésteres de

boronato quirales, y diferentes aldehídos derivados de serina L y D, se pueden obtener todos los posibles diaestereómeros de las 5-alquil-, 4-hidroxil-, y 3-amino-piperidinas trisustituidas resultantes. La reacción de la piperidina sustituida XIV con 4-cloro-3-nitro-piridina, seguida por protección de carbamato, reducción de nitro, acoplamiento de amida, abertura de carbamato cíclico, y desprotección, proporcionan las 5-metil-, 4-hidroxil-, 3-amino-piperidinil-tiazol-amidas trisustituidas XII. Si R_2 es halógeno o triflato, la amida XII se puede modificar adicionalmente mediante modificaciones convencionales para introducir 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 con reactivos organometálicos, o mediante la conversión hasta el éster de boronato correspondiente y la reacción con haluros de arilo/heteroarilo o triflatos, son posibles una variedad de modificaciones de R_2.

Esquema 4



Los compuestos de la invención son útiles *in vitro* 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 aquéllos 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

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en la materia. Véase, por ejemplo, Prescott, Editor, *Methods in Cell Biology*, Volumen XIV, Academic Press, Nueva York, N.W., 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 el 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.

La presente invención se entenderá más fácilmente haciendo referencia a los siguientes ejemplos, los cuales se proporcionan a manera de ilustración y no pretenden ser limitantes de la presente invención.

Las cadenas laterales representativas para utilizarse en los compuestos de los siguientes ejemplos se pueden preparar en términos generales de acuerdo con los siguientes procedimientos:

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 periodo 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 periodo 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 GCMS se llevó a cabo en un instrumento Hewlett Packard (cromatógrafo de gas Serie HP6890 con un Detector

Selectivo de Masa 5973; volumen del inyector: 1 microlitro; temperatura inicial de la columna: 50°C; temperatura final de la columna: 250°C; tiempo de rampa: 20 minutos; velocidad de flujo de gas: 1 *mililitro/minuto*; columna: *fenil-metil-siloxano al 5 por ciento*, Modelo No. HP 190915-443, dimensiones: 30.0 metros x 25 metros x 0.25 metros).

El análisis de resonancia magnética nuclear (RMN) se puede llevar a cabo con un Varian de RMN de 300 ó 400 MHz (Palo Alto, CA). La referencia espectral puede ser TMS o bien el cambio químico conocido del solvente.

La pureza de algunos de los compuestos se evalúa mediante análisis elemental (Desert Analytics, Tucson, AZ).

Los puntos de fusión se determinan en un aparato Laboratory Devices Mel-Temp (Holliston, MA).

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, amoniaco acuoso (o hidróxido de amonio), y trietil-amina. Los solventes típicos

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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

Boc_2O	dicarbonato de di-terbutilo
DAST	trifluoruro de (dietil-amino)-azufre
DCM	dicloro-metano
DIEA	di-isopropil-etil-amina

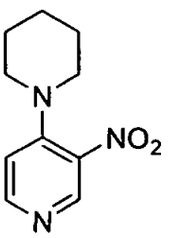
DtBAD	azodicarboxilato de diterbutilo
DMA	dimetil-acetamida
DMAP	4-dimetil-amino-piridina
DME	1,2-dimetoxi-etano
DMF	*N*,*N*-dimetil-formamida
DPPF	1,1'-bis-(difenil-fosfino)-ferroceno
EDC	clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida
EtOAc	acetato de etilo
EtOH	etanol
HOAT	hidroxi-azabenzotriazol
MeCN	acetonitrilo
MeOH	metanol
Na_2CO_3	carbonato de sodio
$NaHCO_3$	bicarbonato de sodio
NBS	*N*-bromo-succinimida
NMP	*N*-metil-2-pirrolidona

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$Pd_2(dba)_3$	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
TDMSCl	Cloruro de terbutil-dimetil-sililo
TEA	trietil-amina
THF	tetrahidrofurano
Tf2O	Anhídrido tríflico

Método 1

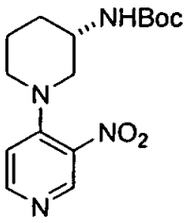
Síntesis de 3-nitro-4-(piperidin-1-il)-piridina



Una solución de 4-cloro-3-nitro-piridina (1.0 equivalentes) y piperidina (2.0 equivalentes) en etanol, en una concentración de 0.5M, se agitó a temperatura ambiente durante 48 horas, en cuyo tiempo, se removió el etanol al vacío. El residuo se dividió entre

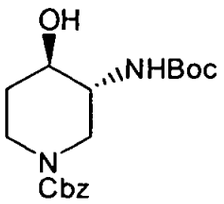
EtOAc (300 mililitros) y Na_2CO_3 saturado (75 mililitros), se lavó adicionalmente con H_2O (50 mililitros), NaCl saturado (50 mililitros), se secó sobre $MgSO_4$, se filtró y los volátiles se removieron al vacío, proporcionando la 3-nitro-4-(piperidin-1-il)-piridina (95 por ciento). LCMS (*m/z*): 207.7 (MH^+); LC R_t = 1.60 minutos. ^1H RMN ($CDCl_3$): δ 8.80 (s, 1H), 8.31 (d, J=5.7, 1H), 6.84 (d, J=6.3, 1H), 3.18-3.21 (m, 4H), 1.64-1.78 (m, 6H).

Síntesis de 1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de (S)-terbutilo



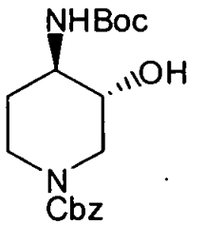
Se siguió el Método 1 utilizando 1 equivalente de cada uno de 4-cloro-3-nitro-piridina, (S)-3-N-Boc-amino-piperidina, y di-isopropil-etil-amina, proporcionando el 1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de (S)-terbutilo, (99 por ciento). LCMS (*m/z*): 323.1 (MH^+); LC R_t = 2.13 minutos.

Síntesis de trans-(+/-)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo



Síntesis de trans-(+/-)-4-(terbutoxi-carbonil-amino)-3-hidroxi-

piperidin-1-carboxilato de bencilo

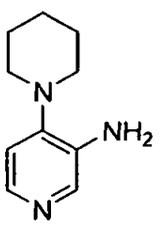


Una solución de (+/-)-7-oxa-3-azabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo (1.0 equivalentes) en una solución acuosa saturada de hidróxido de amonio y etanol (1:1, solución 0.05 M) en una bomba de acero sellada se calentó a 70°C durante 5 horas. Después de que se removieron todos los materiales volátiles mediante corriente de gas de N_2, se agregaron acetato de etilo y agua para el procesamiento. La mezcla regioisomérica cruda de 3-amino-4-hidroxi-piperidin-1-carboxilato de bencilo y 4-amino-3-hidroxi-piperidin-1-carboxilato de bencilo se hizo reaccionar con Boc_2O (1.0 equivalentes) y trietil-amina (1.0 equivalentes) en diclorometano (solución 0.1 M). Después de agitarse durante 2 horas a temperatura ambiente, la mezcla de reacción se extrajo con diclorometano. El (+/-)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo polar y el (+/-)-4-(terbutoxi-carbonil-amino)-3-hidroxi-piperidin-1-carboxilato de bencilo no polar, se obtuvieron mediante cromatografía en columna por evaporación instantánea (del 20 por ciento al 40 por ciento de EtOAc en hexanos, 28 por ciento, 51 por ciento de cada uno). LCMS (*m/z*): 351.1 (MH^+), R_t = 0.81 minutos, LCMS (*m/z*): 351.1 (MH^+), R_t = 0.83 minutos. El (3*S*,4*S*)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo

y el (3*R*,4*R*)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo enantioméricamente puros se resolvieron mediante HPLC quiral (para el análisis: R_t = 6.8 minutos y 9.1 minutos, respectivamente; n-heptano:etanol = 70:30 (volumen : volumen), Chiralpak AD-H de preparación, 250 X 4.6 milímetros a 1 mililitro/minuto. Para la separación de preparación: n-heptano:etanol = 80:20 (volumen : volumen), Chiralpak AS 50 x 500 milímetros a 90 mililitros/minuto).

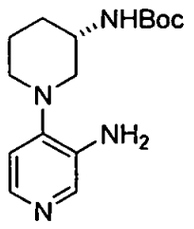
Método 2

Síntesis de 4-(piperidin-1-il)-piridin-3-amina



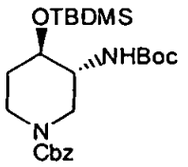
A una solución de la 3-nitro-4-(piperidin-1-il)-piridina (1.0 equivalentes) en etanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 15 horas. En este tiempo la mezcla se filtró a través de un cojín de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la 4-(piperidin-1-il)-piridin-3-amina (93 por ciento) como un aceite. LCMS (*m/z*): 178.0 (MH^+); LC R_t = 1.68 minutos. ^1H RMN ($CDCl_3$): δ 8.01 (s, 1H), 7.96 (d, J=5.4, 1H), 6.78 (d, J=5.1, 1H), 3.64-3.74 (m, 2H), 2.86-2.94 (m, 4H), 1.66-1.78 (m, 4H), 1.58-1.64 (m, 2H).

Síntesis de (S)-1-(3-amino-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, el (S)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo, proporcionando el (S)-1-(3-amino-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, (78 por ciento). LCMS (*m/z*): 293.1 (MH^+); LC R_t = 2.08 minutos.

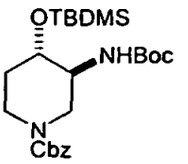
Síntesis de (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo



A una solución del (3*R*,4*R*)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en dicloro-metano (solución 0.1 M), se le agregaron imidazol (1.1 equivalentes), DMAP (0.1 equivalentes), y TBDMSCl (1.1 equivalentes) en secuencia. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas. Después del procesamiento con dicloro-metano, el material crudo se purificó mediante cromatografía en columna de sílice (del 10 por ciento al 20 por ciento de EtOAc en hexanos), proporcionando el (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de

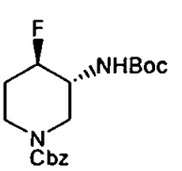
bencilo (76 por ciento). LCMS (*m/z*): 365.2 [(M-Boc)H^+]; LC R_t = 6.05 minutos.

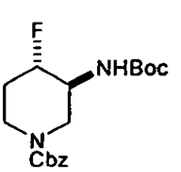
Síntesis de (3S,4S)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo



A una solución del (3*S*,S*R*)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en dicloro-metano (solución 0.1 M), se le agregaron imidazol (1.1 equivalentes), DMAP (0.1 equivalentes), y TBDMSCl (1.1 equivalentes) en secuencia. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas. Después del procesamiento con dicloro-metano, el material crudo se purificó mediante cromatografía en columna de sílice (del 10 por ciento al 20 por ciento de EtOAc en hexanos), proporcionando el (3S,4S)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo. LCMS (*m/z*): 365.2 [(M-Boc)H^+]; LC R_t = 6.05 minutos.

Síntesis de (3*R*,4*R*)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo y (3*S*,4*S*)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo

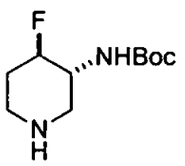




A una solución del (+/-)-3-(terbutoxi-carbonil-amino)-4-hidroxi-

piperidin-1-carboxilato de bencilo (1.0 equivalentes) en diclorometano (solución 0.3 M), se le agregó DAST a -78°C. La mezcla de reacción se calentó lentamente hasta la temperatura ambiente durante 15 horas. Después de apagarse con una solución acuosa saturada de bicarbonato de sodio, se agregaron acetato de etilo y agua para el procesamiento. El (+/-)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo se obtuvo mediante cromatografía en columna de sílice (30 por ciento de EtOAc en hexanos, 40 por ciento). LCMS (*m/z*): 253.1[(M-Boc)H^+]; LC R_t = 4.08 minutos. El (3*R*,4*R*)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo y el (3*S*,4*S*)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo enantioméricamente puros se resolvieron mediante HPLC quiral (para el análisis: R_t = 9.4 minutos y 12.6 minutos, respectivamente; n-heptano:isopropanol = 90:10 (volumen : volumen), Chiralpak AS 250 x 4.6 milímetros a 1 mililitro/minuto. Para la separación de preparación, n-heptano:isopropanol = 90:10 (volumen : volumen), Chiralpak AS 50 x 500 milímetros a 90 mililitros/minuto).

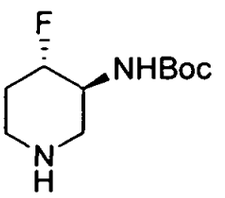
Síntesis de (3R,4R)-4-fluoro-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 2 utilizando el (3R,4R)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo (1.0 equivalentes), proporcionando el (3R,4R)-4-fluoro-piperidin-3-il-

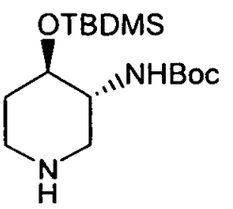
carbamato de terbutilo crudo, (93 por ciento). LCMS (*m/z*): 219.2 (MH^+), LC R_t = 0.45 minutos.

Síntesis de (3S,4S)-4-fluoro-piperidin-3-il-carbamato de terbutilo



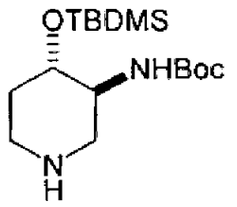
Se siguió el Método 2 utilizando el (3S,4S)-3-(terbutoxi-carbonil-amino)-4-fluoro-piperidin-1-carboxilato de bencilo (1.0 equivalentes), proporcionando el (+/-)-4-fluoro-piperidin-3-il-carbamato de terbutilo crudo, (93 por ciento). LCMS (*m/z*): 219.2 (MH^+), LC R_t = 0.45 minutos.

Síntesis de (3R,4R)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



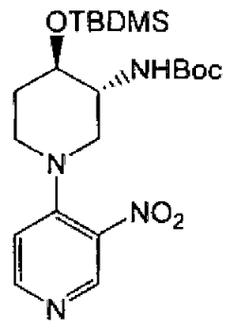
Se siguió el Método 2 utilizando el (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo (1.0 equivalentes), proporcionando el (3R,4R)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo crudo, (>99 por ciento). LCMS (*m/z*): 331.3 (MH^+).

Síntesis de (3R,4R)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



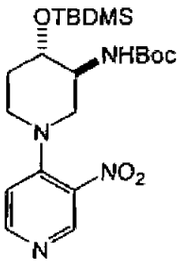
Se siguió el Método 2 utilizando el (3S,4S)-3-(terbutoxi-carbonil-amino)-4-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo (1.0 equivalentes), proporcionando (3S,4S)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo crudo, (>99 por ciento). LCMS (*m/z*): 331.3 (MH^+).

Síntesis de (3R,4R)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



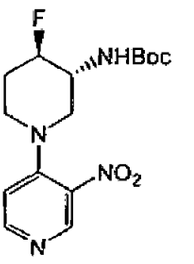
Se siguió el Método 1 utilizando 1 equivalente de cada uno de 4-cloro-3-nitro-piridina, (3R,4R)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, y trietil-amina en N,N-dimetil-formamida, proporcionando el (3R,4R)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, (98 por ciento). LCMS (*m/z*): 453.3 (MH^+); LC R_t = 4.01 minutos.

Síntesis de (3S,4S)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



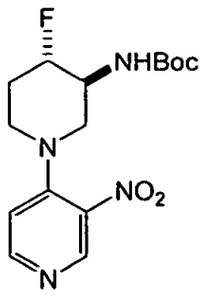
Se siguió el Método 1 utilizando 1 equivalente de cada uno de 4-cloro-3-nitro-piridina, (3S,4S)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, y trietil-amina en N,N-dimetil-formamida, proporcionando el (3S,4S)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, (98 por ciento). LCMS (*m/z*): 453.3 (MH^+); LC R_t = 4.01 minutos.

Síntesis de (3R,4R)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



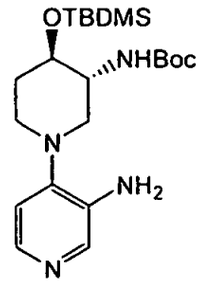
Se siguió el Método 1 del Ejemplo 1, utilizando 1 equivalente de cada uno de 4-cloro-3-nitro-piridina, (3R,4R)-4-fluoro-piperidin-3-il-carbamato de terbutilo, y trietil-amina en etanol, proporcionando el (3R,4R)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, (91 por ciento). LCMS (*m/z*): 341.0 (MH^+); LC R_t = 2.37 minutos.

Síntesis de (3S,4S)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 1 del Ejemplo 1, utilizando 1 equivalente de cada uno de 4-cloro-3-nitro-piridina, (3S,4S)-4-fluoro-piperidin-3-il-carbamato de terbutilo, y trietil-amina en etanol, proporcionando el (3S,4S)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, (91 por ciento). LCMS (*m/z*): 341.0 (MH^+); LC R_t = 2.37 minutos.

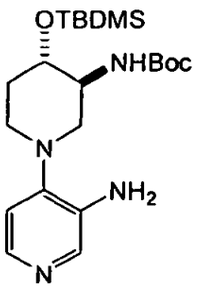
Síntesis de (3R,4R)-1-(3-amino-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, se redujo el (3R,4R)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo en etanol y acetato de etilo (1:1, solución 0.1 M), proporcionando el (3R,4R)-1-(3-amino-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, (>99 por ciento). LCMS (*m/z*): 423.2 (MH^+); LC R_t = 3.78 minutos.

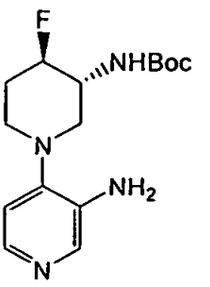
Síntesis de (3S,4S)-1-(3-amino-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-

piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, se redujo el (3R,4R)-4-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo en etanol y acetato de etilo (1:1, solución 0.1 M), proporcionando el (3R,4R)-1-(3-amino-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, (>99 por ciento). LCMS (*m/z*): 423.2 (MH^+); LC R_t = 3.78 minutos.

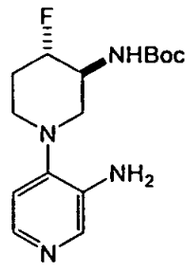
Síntesis de (3R,4R)-1-(3-amino-piridin-4-il)-4-fluoro-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, se redujo el (3R,4R)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo en etanol y acetato de etilo (1:1, solución 0.1 M), proporcionando el (3R,4R)-1-(3-amino-piridin-4-il)-4-fluoro-piperidin-3-il-carbamato de terbutilo, (>99 por ciento). LCMS (*m/z*): 311.2 (MH^+); LC R_t = 2.14 minutos.

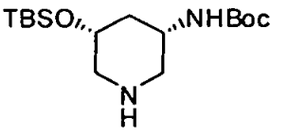
Síntesis de (3S,4S)-1-(3-amino-piridin-4-il)-4-fluoro-piperidin-3-il-

carbamato de terbutilo



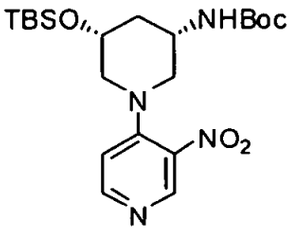
Siguiendo el Método 2, se redujo el (3S,4S)-4-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo en etanol y acetato de etilo (1:1, solución 0.1 M), proporcionando el (3R,4R)-1-(3-amino-piridin-4-il)-4-fluoro-piperidin-3-il-carbamato de terbutilo, (>99 por ciento). LCMS (*m/z*): 311.2 (MH^+); LC R_t = 2.14 minutos.

Síntesis de (3S,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



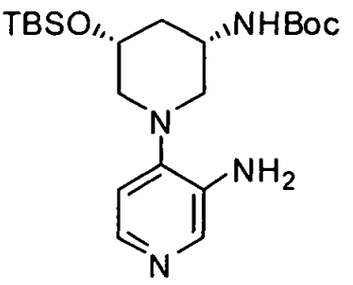
El (3S,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo se preparó de acuerdo con el procedimiento de patente descrito por Y, Zhou; Publicación Internacional Número WO2005028467.

Síntesis de (3S,5R)-5-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



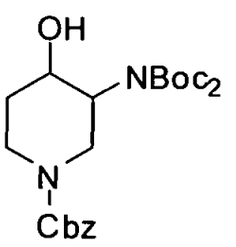
Se siguió el Método 1 utilizando el (3S,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, proporcionando el (3S,5R)-5-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 453.2 (MH^+).

Síntesis de (3S,5R)-1-(3-amino-piridin-4-il)-5-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 2 utilizando el (3S,5R)-5-(terbutil-dimetil-sililoxi)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, proporcionando el (3S,5R)-1-(3-amino-piridin-4-il)-5-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 423.2 (MH^+).

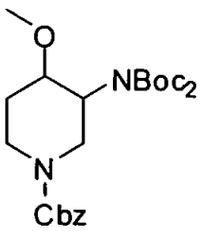
Síntesis de trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo



A una solución del trans-(+/-)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en dicloro-metano y CH_3CN (1:1, 0.14 M), se le agregaron BOC_2O (1.0

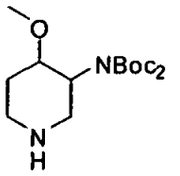
equivalentes), trietil-amina (1.5 equivalentes), y DMAP (cantidad catalítica). La reacción se agitó a temperatura ambiente durante 15 horas, después de cuyo tiempo, la solución se concentró y se purificó mediante cromatografía en columna de gel de sílice, eluyendo con EtOAc y hexanos (1:6), para dar el producto deseado como una espuma blanca. LCMS (*m/z*): 451.1 (MH^+).

Síntesis de trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-metoxi-piperidin-1-carboxilato de bencilo



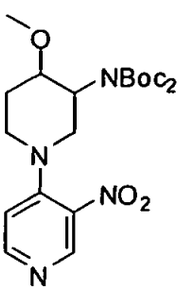
A una solución de NaH (1.3 equivalentes) en tetrahidrofurano (0.1M), se le agregó el 3-(bis-(terbutoxi-carbonil)-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes), y la reacción se calentó a 50°C durante 10 minutos. Después de enfriarse a temperatura ambiente, se agregó MeI (1.5 equivalentes), y la solución se dejó agitándose durante 16 horas. La reacción se apagó con agua, entonces se extrajo con EtOAc, la fase orgánica se secó con salmuera y Na_2SO_4, y se concentró. El material crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con EtOAc y hexanos (1:3), para dar un aceite transparente en un 71 por ciento de rendimiento. LCMS (*m/z*): 365.0 (MH^+).

Síntesis de trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-metoxi-piperidina



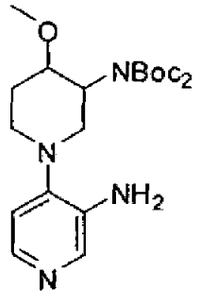
Se siguió el Método 2 utilizando el trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-metoxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes), proporcionando la trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-metoxi-piperidina cruda que se utilizó para el siguiente paso sin mayor purificación. LCMS (*m/z*):331.2 (MH^+)

Síntesis de trans-(+/-)-N,N-di-BOC-4-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-amina



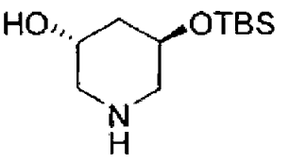
Se siguió el Método 1 utilizando la trans-(+/-)-3-(bis-(terbutoxi-carbonil)-amino)-4-metoxi-piperidina (1.0 equivalentes), 4-cloro-3-nitro-piridina (1.2 equivalentes), y DIEA (4.0 equivalentes), para dar la trans-(+/-)-N,N-di-BOC-4-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-amina después de la cromatografía en columna (EtOAc y hexanos, 50 por ciento) en un 59 por ciento de rendimiento en dos pasos. LCMS (*m/z*): 453.2 (MH^+), LC R_t = 3.24 minutos.

Síntesis de trans-(+/-)-N,N-di-BOC-4-metoxi-1-(3-amino-piridin-4-il)-piperidin-3-amina



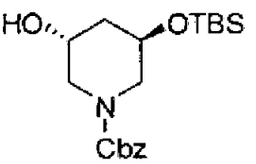
Se siguió el Método 2 utilizando la trans-(+/-)-N,N-di-BOC-4-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-amina, para dar la trans-(+/-)-N,N-di-BOC-4-metoxi-1-(3-amino-piridin-4-il)-piperidin-3-amina en un >95 por ciento de rendimiento como un aceite transparente. LCMS (*m/z*): 423.0 (MH^+), LC R_t = 3.10 minutos.

Síntesis de (3R,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-ol



El (3R,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-ol se preparó de acuerdo con el procedimiento de patente descrito por Zhou, Y. Publicación Internacional Número WO2005028467.

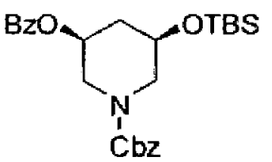
Síntesis de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-hidroxi-piperidin-1-carboxilato de bencilo



A una solución del (3R,5R)-5-(terbutil-dimetil-sililoxi)-piperidin-3-ol (1 equivalente) en 20 mililitros de 1,4-dioxano y 8 mililitros de agua, se le agregó cloroformato de bencilo (1.5 equivalentes). La

mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla cruda se diluyó con 100 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacio. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 3), para proporcionar el (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-hidroxi-piperidin-1-carboxilato de bencilo (74 por ciento). LC/MS (*m/z*): 366.2 (MH^+).

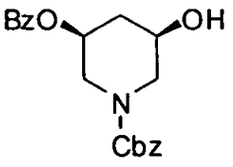
Síntesis de (3S,5R)-3-(benzoiloxi)-5-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo



A una solución en agitación a 0°C de trifenil-fosfina (1.2 equivalentes) en 23 mililitros de tetrahidrofurano, se le agregó azodicarboxilato de diterbutilo (1.2 equivalentes). La mezcla se agitó a 0°C durante 10 minutos. Entonces se agregó una solución de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en 11 mililitros de tetrahidrofurano, y se agitó durante 20 minutos a 0°C. Entonces se agregó ácido benzoico (1.2 equivalentes), y la mezcla de reacción se dejó calentar lentamente a temperatura ambiente. Después de 16 horas, la mezcla de reacción se concentró al vacío, entonces se diluyó con EtOAc, y se lavó con agua y luego con salmuera. La capa orgánica se secó

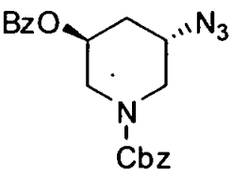
con Na_2SO_4, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 8), para proporcionar el (3S,5R)-3-(benzoiloxi)-5-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo (77 por ciento). LC/MS (*m/z*): 470.2 (MH^+), HPLC R_t = 6.05 minutos.

Síntesis de (3S,5R)-3-(benzoiloxi)-5-hidroxi-piperidin-1-carboxilato de bencilo



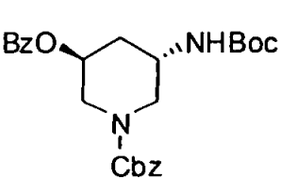
A una solución del (3S,5R)-3-(benzoiloxi)-5-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo (1 equivalente) en 30 mililitros de metanol, se le agregó HCl 3.8M en isopropanol (4 equivalentes). La mezcla de reacción se dejó reposar a temperatura ambiente durante 3 horas, en cuyo punto, se concentró bajo presión reducida. El residuo resultante se diluyó con 120 mililitros de EtOAc, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-3-(benzoiloxi)-5-hidroxi-piperidin-1-carboxilato de bencilo (95 por ciento). LC/MS (*m/z*): 355.9 (MH^+). HPLC: R_t: 3.62 minutos.

Síntesis de (3S,5S)-3-azido-5-(benzoiloxi)-piperidin-1-carboxilato de bencilo



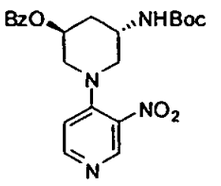
A una solución del (3S,5R)-3-(benzoiloxi)-5-hidroxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 20 mililitros de diclorometano se le agregaron trietil-amina (3 equivalentes) y cloruro de metan-sulfonilo (1.5 equivalentes) a 0°C. La mezcla de reacción se dejó agitándose a temperatura ambiente durante 2 horas. La mezcla cruda se diluyó con 120 mililitros de EtOAc, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se disolvió en 25 mililitros de NMP. Se agregó azida de sodio (2.2 equivalentes), y la suspensión resultante se agitó a 80°C durante la noche. La mezcla de reacción se diluyó con 200 mililitros de EtOAc y 100 mililitros de hexanos, se lavó con agua, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 2), para proporcionar el (3S,5S)-3-azido-5-(benzoiloxi)-piperidin-1-carboxilato de bencilo (88 por ciento). LC/MS (*m/z*): 381.0 (MH^+). HPLC: R_t: 4.41 minutos.

<u>Síntesis de (3S,5S)-3-(benzoiloxi)-5-(terbutoxi-carbonil-amino)-piperidin-1-carboxilato de bencilo</u>



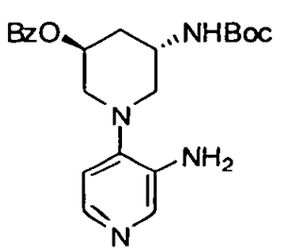
A una solución del (3S,5S)-3-azido-5-(benzoiloxi)-piperidin-1-carboxilato de bencilo (1 equivalente) en una mezcla de 14 mililitros de piridina y 2 mililitros de hidróxido de amonio, se le agregó trimetil-fosfina 1M (3 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 3 horas, en cuyo punto, los solventes se removieron bajo presión reducida, para dar un aceite amarillo. El aceite se disolvió nuevamente en 100 mililitros de etanol, y se concentró para remover el hidróxido de amonio completamente. El residuo se disolvió en 24 mililitros de 1,4-dioxano, y se agregaron 24 mililitros de $NaHCO_3$ acuoso saturado. Se agregó por goteo dicarbonato de diterbutilo (4 equivalentes) en 12 mililitros de tetrahidrofurano a 0°C. La mezcla se dejó agitándose a temperatura ambiente durante 2 horas. La mezcla cruda se diluyó con 200 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 2), para proporcionar el (3S,5S)-3-(benzoiloxi)-5-(terbutoxi-carbonil-amino)-piperidin-1-carboxilato de bencilo (92 por ciento). LC/MS (*m/z*): 455.1 (MH^+). HPLC: R_t: 4.38 minutos.

<u>Síntesis de (3S,5S)-benzoato de 5-(terbutoxi-carbonil-amino)-1-(3-nitro-piridin-4-il)-piperidin-3-ilo</u>



A una solución del (3S,5S)-3-(benzoiloxi)-5-(terbutoxi-carbonil-amino)-piperidin-1-carboxilato de bencilo (1 equivalente) en 15 mililitros de metanol y 15 mililitros de EtOAc, se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante 4 horas. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 20 mililitros de isopropanol, y se agregaron di-isopropil-etil-amina (1.8 equivalentes) y 4-cloro-3-nitro-piridina (1.2 equivalentes). La mezcla de reacción se agitó a 75°C durante 2 horas, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 150 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5S)-benzoato de 5-(terbutoxi-carbonil-amino)-1-(3-nitro-piridin-4-il)-piperidin-3-ilo (90 por ciento). LC/MS (*m/z*): 443.2 (MH^+). HPLC: R_t: 2.89 minutos.

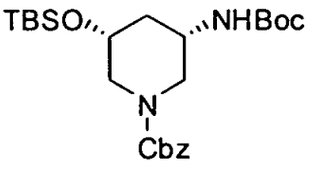
Síntesis de (3S,5S)-benzoato de 1-(3-amino-piridin-4-il)-5-(terbutoxi-carbonil-amino)-piperidin-3-ilo



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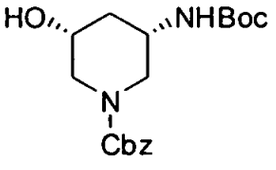
Siguiendo el Método 2, el (3S,5S)-benzoato de 5-(terbutoxi-carbonil-amino)-1-(3-nitro-piridin-4-il)-piperidin-3-ilo se redujo para proporcionar el (3S,5S)-benzoato de 1-(3-amino-piridin-4-il)-5-(terbutoxi-carbonil-amino)-piperidin-3-ilo. LC/MS (*m/z*): 413.1 (MH^+). HPLC: R_t: 2.75 minutos.

Síntesis de (3S,5R)-3-(terbutoxi-carbonil-amino)-5-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo



Se siguió el método para la síntesis del (3S,5S)-3-(benzoiloxi)-5-(terbutoxi-carbonil-amino)-piperidin-1-carboxilato de bencilo, empezando a partir del (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-hidroxi-piperidin-1-carboxilato de bencilo. LC/MS (*m/z*): 365.2 (MH^+-Boc), Rt: 1.37.

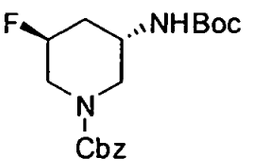
Síntesis de (3S,5R)-3-(terbutoxi-carbonil-amino)-5-hidroxi-piperidin-1-carboxilato de bencilo



A una solución del (3S,5R)-3-(terbutoxi-carbonil-amino)-5-(terbutil-dimetil-sililoxi)-piperidin-1-carboxilato de bencilo (1 equivalente) en 30 mililitros de tetrahidrofurano, se le agregaron 5.2 mililitros de TBAF (1.2 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se diluyó con

acetato de etilo, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (metanol al 5 por ciento en EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-3-(terbutoxi-carbonil-amino)-5-hidroxi-piperidin-1-carboxilato de bencilo (100 por ciento). LC/MS (*m/z*): 251.2 (MH^+), Rt: 0.89. HPLC: R_t: 3.26 minutos.

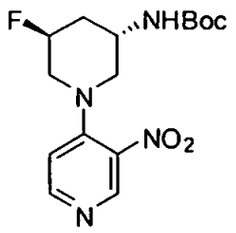
Síntesis de (3S,5S)-3-(terbutoxi-carbonil-amino)-5-fluoro-piperidin-1-carboxilato de bencilo



A una solución del (3S,5R)-3-(terbutoxi-carbonil-amino)-5-hidroxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 5 mililitros de dicloro-metano se le agregó DAST (1.35 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se diluyó con 120 mililitros de acetato de etilo, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 3), para proporcionar (3S,5S)-1-(3-amino-piridin-4-il)-5-fluoro-piperidin-3-il-carbamato de terbutilo (30 por ciento). LC/MS (*m/z*): 253.1 (MH^+-100), R_t = 0.96 minutos. HPLC: R_t: 3.79 minutos.

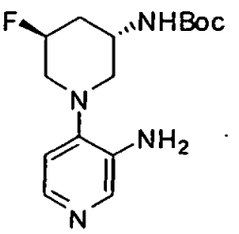
Síntesis de (3S,5S)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo

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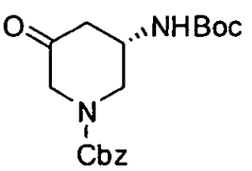
A una solución del (3S,5S)-3-(terbutoxi-carbonil-amino)-5-fluoro-piperidin-1-carboxilato de bencilo (1 equivalente) en 5 mililitros de metanol y 5 mililitros de EtOAc, se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante 4 horas. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 5 mililitros de isopropanol, y se agregaron di-isopropil-etil-amina (1.8 equivalentes) y 4-cloro-3-nitro-piridina (1.5 equivalentes). La mezcla de reacción se agitó a 65°C durante 3 horas, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 120 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para dar el (3S,5S)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (78 por ciento). LC/MS (*m/z*): 341.1 (MH^+), R_t = 0.57 minutos. HPLC: R_t: 2.01 minutos.

Síntesis de (3S,5S)-1-(3-amino-piridin-4-il)-5-fluoro-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, el (3S,5S)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo para proporcionar el (3S,5S)-1-(3-amino-piridin-4-il)-5-fluoro-piperidin-3-il-carbamato de terbutilo.. LC/MS (*m/z*): 311.1 (MH^+), R_t = 0.54 minutos. HPLC: R_t: 1.76 minutos.

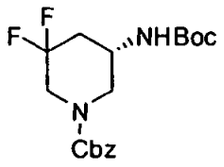
Síntesis de (S)-3-(terbutoxi-carbonil-amino)-5-oxo-piperidin-1-carboxilato de bencilo



A una solución del (3S,5R)-3-(terbutoxi-carbonil-amino)-5-hidroxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 10 mililitros de dicloro-metano, se le agregó peryodinano Dess-Martin (1.2 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a esa temperatura durante la noche. La mezcla se diluyó con acetato de etilo, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 2), para proporcionar el (S)-3-(terbutoxi-carbonil-amino)-5-oxo-piperidin-1-carboxilato de bencilo (81 por ciento). LC/MS (*m/z*): 249.1 (MH^+-100), R_t: 0.83 minutos. HPLC: R_t: 3.26

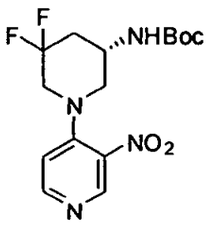
minutos.

Síntesis de 5-(terbutoxi-carbonil-amino)-3,3-difluoro-piperidin-1-carboxilato



A una solución del (S)-3-(terbutoxi-carbonil-amino)-5-oxo-piperidin-1-carboxilato de bencilo (1 equivalente) en 25 mililitros de dicloro-metano, se le agregó DAST (20 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La reacción se apagó mediante bicarbonato de sodio acuoso. La mezcla resultante se extrajo con acetato de etilo. La capa orgánica se separó y se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 2), para proporcionar el 5-(terbutoxi-carbonil-amino)-3,3-difluoro-piperidin-1-carboxilato (52 por ciento). LC/MS (*m/z*): 271.1 (-Boc), R_t: 0.99min.

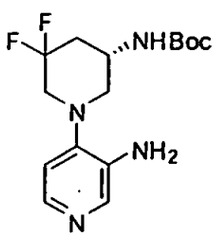
Síntesis de (S)-5,5-difluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



A una solución del 5-(terbutoxi-carbonil-amino)-3,3-difluoro-

piperidin-1-carboxilato (1 equivalente) en 5 mililitros de metanol y 5 mililitros de EtOAc, se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó bajo una atmósfera de H_2 durante la noche. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 5 mililitros de isopropanol, y se agregaron di-isopropil-etil-amina (2.0 equivalentes) y 4-cloro-3-nitro-piridina (1.5 equivalentes). La mezcla de reacción se agitó a 70°C durante 3 horas, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 120 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (metanol al 5 por ciento en EtOAc : hexanos = 1 : 1), para proporcionar el (S)-5,5-difluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (19 por ciento). LC/MS (*m/z*): 359.0 (MH^+), R_t: 0.65 minutos.

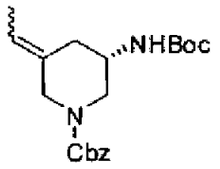
<u>Síntesis de (S)-1-(3-amino-piridin-4-il)-5,5-difluoro-piperidin-3-il-carbamato de terbutilo</u>



Siguiendo el Método 2, el (S)-5,5-difluoro-1-(3-nitro-piridin-4-

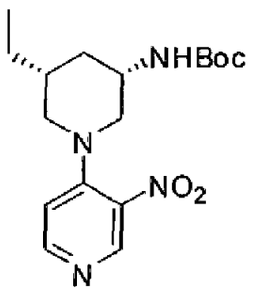
il)-piperidin-3-il-carbamato de terbutilo se redujo para proporcionar el (S)-1-(3-amino-piridin-4-il)-5,5-difluoro-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 329.0 (MH^+), R_t: 0.62 minutos.

Síntesis de (S)-3-(terbutoxi-carbonil-amino)-5-etiliden-piperidin-1-carboxilato de bencilo



A una suspensión de bromuro de etil-trifenil-fosfonio (11 equivalentes) en 14 mililitros de tetrahidrofurano, se le agregó terbutóxido de potasio (10 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a esa temperatura durante 20 minutos. Entonces la reacción se enfrió a 0°C, y se agregó (S)-3-(terbutoxi-carbonil-amino)-5-oxo-piperidin-1-carboxilato de bencilo (1 equivalente) en 7 mililitros de tetrahidrofurano a la mezcla de reacción. La reacción se dejó calentar hasta la temperatura ambiente. Después de agitarse durante 40 minutos, la mezcla de reacción se vertió en bicarbonato de sodio acuoso, y se extrajo con acetato de etilo. La capa orgánica se separó y se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 2 : 1), para proporcionar el (S)-3-(terbutoxi-carbonil-amino)-5-etiliden-piperidin-1-carboxilato de bencilo. LC/MS (*m/z*): 261.2 (MH^+-100), R_t: 1.12 minutos. HPLC: R_t: 4.31 minutos.

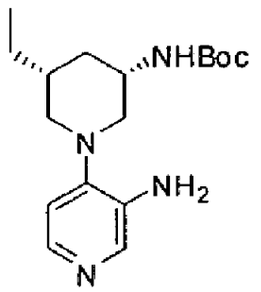
Síntesis de (3S,5R)-5-etil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



A una solución del (S)-3-(terbutoxi-carbonil-amino)-5-etiliden-piperidin-1-carboxilato de bencilo (1 equivalente) en 5.5 mililitros de etanol y 5.5 mililitros de EtOAc, se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante 45 minutos. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 1.4 mililitros de isopropanol, y se agregaron di-isopropil-etil-amina (2.5 equivalentes) y 4-cloro-3-nitro-piridina (1.5 equivalentes). La mezcla de reacción se agitó a 80°C durante la noche, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 120 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-5-etil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (91 por ciento). LC/MS (*m/z*): 351.2 (MH^+), R_t:

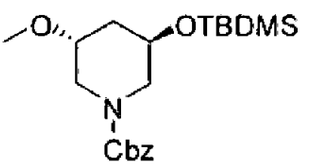
0.75 minutos.

Síntesis de (3S,5R)-1-(3-amino-piridin-4-il)-5-etil-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, el (3S,5R)-5-etil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo para proporcionar el (3S,5R)-1-(3-amino-piridin-4-il)-5-etil-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 321.2 (MH^+), R_t: 0.73 minutos. HPLC: R_t: 2.65 minutos.

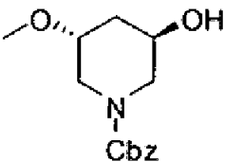
Síntesis de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-metoxi-piperidin-1-carboxilato de bencilo



A una solución de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-hidroxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 30 mililitros de tetrahidrofurano se le agregó hidruro de sodio (1.5 equivalentes), seguido por yoduro de metilo (5 equivalentes) a 0°C. La mezcla de reacción se dejó agitándose a temperatura ambiente durante 3 horas. La mezcla cruda se diluyó con 120 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se

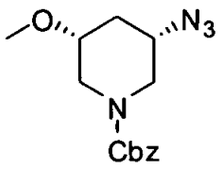
concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 5), para proporcionar el (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-metoxi-piperidin-1-carboxilato de bencilo (93 por ciento). LC/MS (*m/z*): 380.2 (MH^+).

Síntesis de (3R,5R)-3-hidroxi-5-metoxi-piperidin-1-carboxilato de bencilo



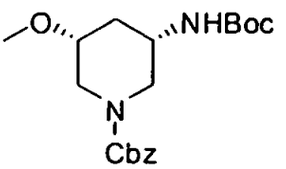
A una solución de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-metoxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 30 mililitros de metanol, se le agregó HCl 3.8M en isopropanol (4 equivalentes). La mezcla de reacción se dejó reposar a temperatura ambiente durante 3 horas, en cuyo punto, se concentró bajo presión reducida. El residuo resultante se diluyó con 100 mililitros de EtOAc, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 2 : 1), para proporcionar el (3R,5R)-3-hidroxi-5-metoxi-piperidin-1-carboxilato de bencilo (92 por ciento). LC/MS (*m/z*): 266.2 (MH^+).

Síntesis de (3S,5R)-3-azido-5-metoxi-piperidin-1-carboxilato de bencilo



A una solución de (3R,5R)-3-hidroxi-5-metoxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 40 mililitros de dicloro-metano se le agregó trietil-amina (3 equivalentes) y cloruro de metan-sulfonilo (1.5 equivalentes) a 0°C. La mezcla de reacción se dejó agitándose a temperatura ambiente durante 2 horas. La mezcla cruda se diluyó con 150 mililitros de EtOAc, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para dar el intermediario, el cual se disolvió en 15 mililitros de N,N-dimetil-formamida. Se agregó azida de sodio (3.3 equivalentes), y la suspensión resultante se agitó a 80°C durante la noche. La mezcla de reacción se diluyó con 150 mililitros de EtOAc, se lavó con agua, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 2), para proporcionar el (3S,5R)-3-azido-5-metoxi-piperidin-1-carboxilato de bencilo (95 por ciento). LC/MS (*m/z*): 263.2 (MH^+-28).

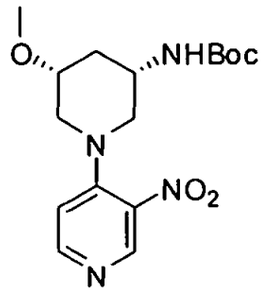
Síntesis de (3S,5R)-3-(terbutoxi-carbonil-amino)-5-metoxi-piperidin-1-carboxilato de bencilo



A una solución del (3S,5R)-3-azido-5-metoxi-piperidin-1-carboxilato de bencilo (1 equivalente) en una mezcla de 14 mililitros de piridina y 2 mililitros de hidróxido de amonio, se le agregó trimetil-fosfina 1M (3 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 4 horas, en cuyo punto, los solventes se removieron bajo presión reducida, para dar un aceite amarillo. El aceite se disolvió nuevamente en 100 mililitros de etanol, y se concentró para remover el hidróxido de amonio completamente. El residuo se disolvió en 16 mililitros de 1,4-dioxano y se le agregaron 16 mililitros de $NaHCO_3$ acuoso saturado. Se agregó por goteo dicarbonato de diterbutilo (4 equivalentes) en 8 mililitros de tetrahidrofurano a 0°C. La mezcla se dejó agitándose a temperatura ambiente durante 2 horas. La mezcla cruda se diluyó con 300 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-3-(terbutoxi-carbonil-amino)-5-metoxi-piperidin-1-carboxilato de bencilo (86 por ciento). LC/MS (*m/z*): 365.0 (MH^+).

Síntesis de (3S,5R)-5-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo

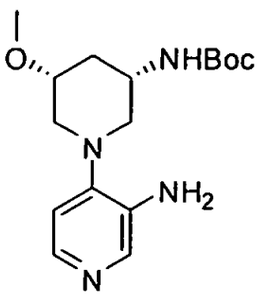
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A una solución del (3S,5R)-3-(terbutoxi-carbonil-amino)-5-metoxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 25 mililitros de metanol, se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante 2 horas. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 25 mililitros de isopropanol, y se agregaron DIEA (1.8 equivalentes) y 4-cloro-3-nitro-piridina (1.2 equivalentes). La mezcla de reacción se agitó a 80°C durante 4 horas, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 150 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (metanol al 5 por ciento en EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-5-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (88 por ciento). LC/MS (*m/z*): 353.0 (MH^+). HPLC: R_t: 2.15 minutos.

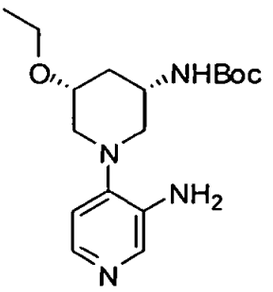
Síntesis de (3S,5R)-1-(3-amino-piridin-4-il)-5-metoxi-piperidin-3-il-

carbamato de terbutilo



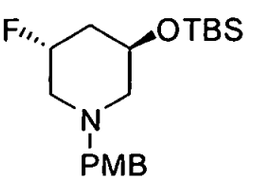
Siguiendo el Método 2, el (3S,5R)-5-metoxi-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo, proporcionando el (3S,5R)-1-(3-amino-piridin-4-il)-5-metoxi-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 323.1 (MH^+).

Síntesis de (3S,5R)-1-(3-amino-piridin-4-il)-5-etoxi-piperidin-3-il-carbamato de terbutilo



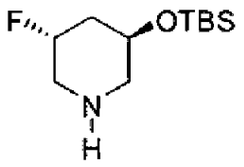
El procedimiento para preparar este compuesto es el mismo que para el compuesto de metoxilo. LC/MS (*m/z*): 337.1 (MH^+), R_t: 0.63 minutos. HPLC: R_t: 2.47 minutos.

Síntesis de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-1-(4-metoxi-bencil)-piperidina



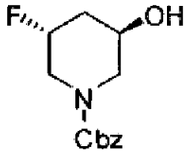
La (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-1-(4-metoxi-bencil)-piperidina se preparó de acuerdo con el procedimiento de la literatura como es descrito por Cossy, J. *Synlett*, **2007**, 263.

Síntesis de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-piperidina



A una solución de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-1-(4-metoxi-bencil)-piperidina (1 equivalente) en 5 mililitros de metanol se le agregó Pd/C al 10 por ciento (0.2 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante la noche. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío, para proporcionar la (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-piperidina, el cual se utilizó para el siguiente paso sin mayor purificación. LC/MS (*m/z*): 234.1 (MH^+).

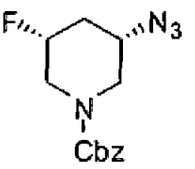
Síntesis de (3R,5R)-3-fluoro-5-hidroxi-piperidin-1-carboxilato de bencilo



A una solución de (3R,5R)-3-(terbutil-dimetil-sililoxi)-5-fluoro-piperidina (1 equivalente) en 30 mililitros de metanol se le agregó HCl 3.8M en isopropanol (4 equivalentes). La mezcla de reacción se dejó reposar a temperatura ambiente durante 3 horas, en cuyo punto,

se concentró bajo presión reducida. El residuo resultante se diluyó con 120 mililitros de EtOAc, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 2 : 1), para dar el (3R,5R)-3-fluoro-5-hidroxi-piperidin-1-carboxilato de bencilo, (94 por ciento). LC/MS (*m/z*): 254.2 (MH^+).

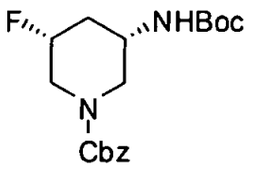
Síntesis de (3S,5R)-3-azido-5-fluoro-piperidin-1-carboxilato de bencilo



A una solución del (3R,5R)-3-fluoro-5-hidroxi-piperidin-1-carboxilato de bencilo (1 equivalente) en 14 mililitros de dicloro-metano se le agregaron trietil-amina (3 equivalentes) y cloruro de metan-sulfonilo (1.5 equivalentes) a 0°C. La mezcla de reacción se dejó agitándose a temperatura ambiente durante 1.5 horas. La mezcla cruda se diluyó con 120 mililitros de dietil-éter, se lavó con bicarbonato de sodio acuoso saturado, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se disolvió en 16 mililitros de NMP. Se agregó azida de sodio (3.0 equivalentes), y la suspensión resultante se agitó a 80°C durante la noche. La mezcla de reacción se diluyó con 200 mililitros de EtOAc y 100 mililitros de hexanos, se lavó con agua, salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al

vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 3), para proporcionar el (3S,5R)-3-azido-5-fluoro-piperidin-1-carboxilato de bencilo (90 por ciento). LC/MS (*m/z*): 251.1 (MH^+-28).

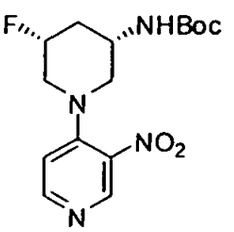
Síntesis de (3S,5R)-3-(terbutoxi-carbonil-amino)-5-fluoro-piperidin-1-carboxilato de bencilo



A una solución del (3S,5R)-3-azido-5-fluoro-piperidin-1-carboxilato de bencilo (1 equivalente) en una mezcla de 11 mililitros de piridina y 1.5 mililitros de hidróxido de amonio, se le agregó trimetil-fosfina 1M (3 equivalentes) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 3 horas, en cuyo punto, los solventes se removieron bajo presión reducida, para dar un aceite amarillo. El aceite se disolvió nuevamente en 100 mililitros de etanol, y se concentró para remover el hidróxido de amonio completamente. El residuo se disolvió en 12 mililitros de 1,4-dioxano, y se agregaron 12 mililitros de $NaHCO_3$ acuoso saturado. Se agregó por goteo dicarbonato de diterbutilo (4 equivalentes) en 6 mililitros de tetrahidrofurano a 0°C. La mezcla se dejó agitándose a temperatura ambiente durante 1 hora. La mezcla cruda se diluyó con 150 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación

instantánea (EtOAc : hexanos = 1 : 1), para proporcionar el (3S,5R)-3-(terbutoxi-carbonil-amino)-5-fluoro-piperidin-1-carboxilato de bencilo (95 por ciento). LC/MS (*m/z*): 253.1 (MH^+-100).

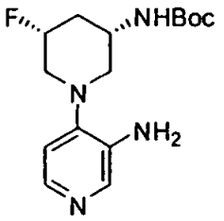
Síntesis de (3S,5R)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



A una solución del (3S,5R)-3-(terbutoxi-carbonil-amino)-5-fluoro-piperidin-1-carboxilato de bencilo (1 equivalente) en 28 mililitros de metanol se le agregó Pd/C al 10 por ciento (0.1 equivalentes). La suspensión resultante se agitó en una atmósfera de H_2 durante 1 hora. Los sólidos crudos se filtraron a través de un cojín de Celite sobre un embudo Buchner revestido de papel, se lavaron con MeOH, y entonces se concentraron al vacío. El residuo se disolvió en 33 mililitros de isopropanol, y se agregaron di-isopropil-etil-amina (2.5 equivalentes) y 4-cloro-3-nitro-piridina (1.5 equivalentes). La mezcla de reacción se agitó a 80°C durante 2 horas, en cuyo punto, la mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró bajo presión reducida. El residuo se diluyó con 150 mililitros de EtOAc, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (metanol al 5 por ciento en EtOAc:hexanos

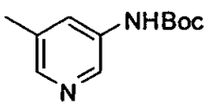
= 1:1), para proporcionar el (3S,5R)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (90 por ciento). LC/MS (*m/z*): 341.1 (MH^+). HPLC: R_t: 2.12 minutos.

Síntesis de (3S,5R)-1-(3-amino-piridin-4-il)-5-fluoro-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, el (3S,5R)-5-fluoro-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo, proporcionando el (3S,5R)-1-(3-amino-piridin-4-il)-5-fluoro-piperidin-3-il-carbamato de terbutilo. LC/MS (*m/z*): 311.1 (MH^+).

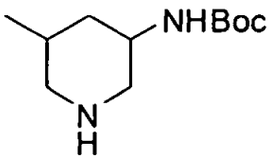
Síntesis de 5-metil-piridin-3-il-carbamato de terbutilo



A una solución de 5-metil-piridin-3-amina (5 gramos, 46 milimoles) en tetrahidrofurano (80 mililitros) a temperatura ambiente, se le agregó bis-(trimetil-silil-amida) de sodio 1M en tetrahidrofurano (101 mililitros, 101 milimoles), se agitó durante 15 minutos, seguida por dicarbonato de diterbutilo (11 gramos, 49 milimoles) en tetrahidrofurano (20 mililitros). La reacción se agitó a temperatura ambiente durante la noche, y se concentró. El concentrado se trató con HCl 0.2M (60 mililitros) y EtOAc, y la capa orgánica se extrajo, se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4, se

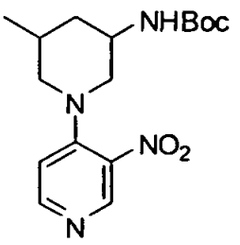
filtró, y se concentró. El concentrado se purificó utilizando cromatografía por evaporación instantánea sobre gel de sílice (40 por ciento de EtOAc : Hexano), para dar un sólido amarillo como el producto de 5-metil-piridin-3-il-carbamato de terbutilo (8.5 gramos, 88 por ciento de rendimiento). LCMS (*m/z*): 209.1 (MH^+); LC R_t = 1.94 minutos. ^1H RMN ($CDCl_3$) δ 8.20(d, 1H), 8.12(s, 1H), 7.86(s, 1H), 6.53(s, 1H), 2.33(s, 3H), 1.53(s, 9H).

Síntesis de cis-(+/-)-5-metil-piperidin-3-il-carbamato de terbutilo



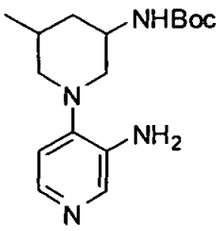
A una solución del 5-metil-piridin-3-il-carbamato (3 gramos, 14 milimoles) en ácido acético helado (50 mililitros), se le agregó rodio al 5 por ciento sobre carbón activado (0.5 gramos) y óxido de platino(IV) (0.5 gramos) en la bomba de acero de hidrogenación. La mezcla se selló y se hidrogenó a 200 psi (14 kg/cm^2) y a 70°C durante 48 horas. La mezcla se filtró a través de Celite, y se concentró para dar el cis-(+/-)-5-metil-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 215.1 (MH^+).

Síntesis de cis-(+/-)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



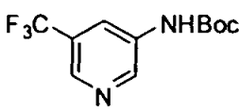
Se siguió el Método 1 utilizando el cis-(+/-)-5-metil-piperidin-3-il-carbamato de terbutilo crudo, proporcionando el cis-(+/-)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (66 por ciento de rendimiento). LCMS (*m/z*): 337.1 (MH^+); LC R_t = 2.50 minutos. ^1H RMN ($CDCl_3$) δ 8.84(s, 1H), 8.36(d, 1H), 7.04(m, 1H), 4.44(m, 1H), 3.90(m, 1H), 3.71(m, 1H), 3.09(d, 1H), 2.66(q, 2H), 2.10(d, 1H), 1.84(m, 1H), 1.56(s, 9H), 0.93(d, 3H).

Síntesis de cis-(+/-)-1-(3-amino-piridin-4-il)-5-metil-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 2 utilizando el cis-(+/-)-5-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, proporcionando el cis-(+/-)-5-metil-1-(3-amino-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (98 por ciento de rendimiento). LCMS (*m/z*): 307.1 (MH^+); LC R_t = 2.44 minutos. ^1H RMN ($CDCl_3$) δ 8.01(s, 1H), 7.95(d, 1H), 6.76(d, 1H), 4.40(m, 1H), 3.70(m, 3H), 3.58(dq, 1H), 3.21(dq, 1H), 2.15(m, 3H), 1.90(m, 1H), 1.58(s, 9H), 0.97(d, 3H).

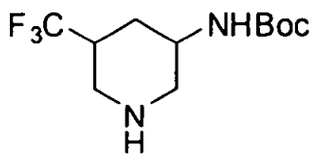
Síntesis de 5-(trifluoro-metil)-piridin-3-il-carbamato de terbutilo



A una solución de la 5-trifluoro-metil-piridin-3-amina (1 equivalente) en tetrahidrofurano (80 mililitros) a temperatura

ambiente, se le agregó bis-(trimetil-silil-amida) de sodio 1M en tetrahidrofurano (2 equivalentes), se agitó durante 15 minutos, seguido por dicarbonato de diterbutilo (1 equivalente) en tetrahidrofurano. La reacción se agitó a temperatura ambiente durante la noche y se concentró. El concentrado se trató con HCl 0.2M acuoso y EtOAc, y la capa orgánica se extrajo, se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El concentrado se purificó utilizando cromatografía por evaporación instantánea sobre gel de sílice (40 por ciento de EtOAc : Hexano), para dar un sólido amarillo como el producto de 5-(trifluoro-metil)-piridin-3-il-carbamato de terbutilo (31 por ciento de rendimiento). LCMS (*m/z*): 263.0 (MH^+); LC R_t = 3.84 minutos. ^1H RMN ($CDCl_3$) δ 8.56(m, 2H), 8.34(s, 1H), 6.71 (s, 1H), 1.55 (s, 9H).

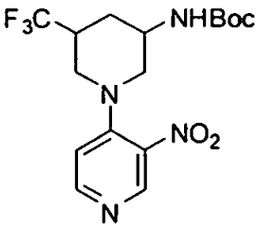
Síntesis de cis-(+/-)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo



A una solución del 5-(trifluoro-metil)-piridin-3-il-carbamato de terbutilo (3 gramos, 14 milimoles) en ácido acético helado (50 mililitros), se le agregó rodio al 5 por ciento sobre carbón activado (0.5 gramos) y óxido de platino(IV) (0.5 gramos) en la bomba de acero de hidrogenación. La mezcla se selló y se hidrogenó a 200 psi (14 kg/cm^2) y a 70°C durante 48 horas. La mezcla se filtró a través de Celite, y se concentró para dar el cis-(+/-)-5-(trifluoro-metil)-

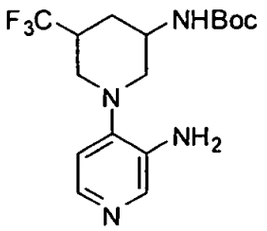
piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 269.1 (MH^+).

Síntesis de cis-(+/-)-1-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 1 utilizando el cis-(+/-)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo crudo, proporcionando el cis-(+/-)-1-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo (42 por ciento de rendimiento en dos pasos). LCMS (*m/z*): 391.1 (MH^+); LC R_t = 2.92 minutos. ^1H RMN ($CDCl_3$) δ 8.93(s, 1H), 8.47(d, 1H), 7.01(d, 1H), 4.50(m, 1H), 3.80(m, 2H), 3.45(m, 1H), 3.00(t, 1H), 2.66(m, 1H), 2.63(m,1H), 2.38(d, 1H), 1.56(s, 9H).

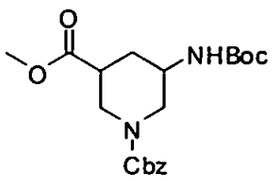
Síntesis cis-(+/-)-1-(3-amino-piridin-4-il)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 2 utilizando el cis-(+/-)-1-(3-nitro-piridin-4-il)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo, proporcionando el cis-(+/-)-1-(3-amino-piridin-4-il)-5-(trifluoro-metil)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 361.0 (MH^+); LC R_t = 2.72 minutos. ^1H RMN ($CDCl_3$) δ 8.05(s, 1H), 7.98(d, 1H), 6.79 (d,

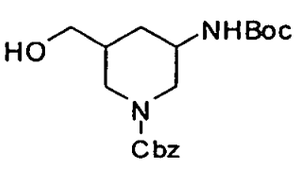
1H), 4.46(m, 1H), 3.83(m, 1H), 3.72(s, 2H), 3.62(m, 1H), 3.49(m, 1H), 2.59(m, 2H), 2.36(m, 1H), 2.23(t,1H), 1.58(s, 9H).

Síntesis de cis-(+/-)-1-3-metil-5-(terbutoxi-carbonil-amino)-piperidin-1,3-dicarboxilato de bencilo



A una solución del cis-(+/-)-ácido 1-(benciloxi-carbonil)-5-(terbutoxi-carbonil-amino)-piperidin-3-carboxílico (1.0 equivalentes), metanol (20 equivalentes) y EDC (1.3 equivalentes) en dicloro-metano en una concentración de 0.25 M a 0°C, se le agregó dimetil-amino-piridina (0.1 equivalentes). Después de agitar durante 48 horas a medida que la reacción se dejó calentar a temperatura ambiente, los volátiles se removieron al vacío. Después de la adición de acetato de etilo, y de lavar con H_2O (3 veces), HCl 1N, $NaHCO_3$ saturado y salmuera, la solución se secó sobre $MgSO_4$, se filtró, se concentró, y se purificó mediante cromatografía en columna (25 por ciento de acetato de etilo/hexanos), para proporcionar el cis-(+/-)-1-3-metil-5-(terbutoxi-carbonil-amino)-piperidin-1,3-dicarboxilato de bencilo. LCMS (*m/z*): 293.1 ($MH\text{-}Boc^+$); LC R_t = 4.09 minutos.

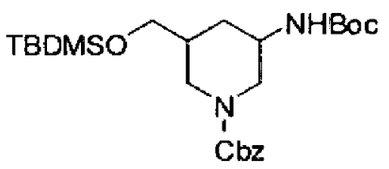
Síntesis de cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(hidroxi-metil)-piperidin-1-carboxilato de bencilo



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Una solución del cis-(+/-)-1-3-metil-5-(terbutoxi-carbonil-amino)-piperidin-1,3-dicarboxilato de bencilo (1.0 equivalentes) en tetrahidrofurano en una concentración de 0.08 M, se enfrió a 0°C, y entonces se agregaron LiCl (2.3 equivalentes) y borohidruro de sodio (2.3 equivalentes). Después de agitar durante 20 horas a medida que la reacción se calentaba a temperatura ambiente, el pH se ajustó con ácido cítrico 1M a un pH de 4 a 5. Después de la remoción de los volátiles al vacío, el producto se extrajo en dicloro-metano, se lavó con H_2O y salmuera, y se secó sobre $MgSO_4$. Después de la filtración y de la remoción de los volátiles al vacío, se obtuvo el cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(hidroxi-metil)-piperidin-1-carboxilato de bencilo como una espuma blanca y sólida. LCMS (*m/z*): 265.0 ($MH-Boc^+$); LC R_t = 3.37 minutos.

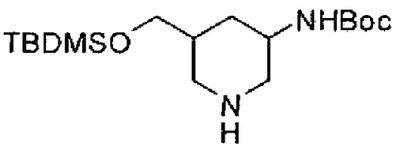
Síntesis de cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-1-carboxilato de bencilo



Una solución del cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(hidroxi-metil)-piperidin-1-carboxilato de bencilo (1.0 equivalentes), imidazol (1.1 equivalentes), cloruro de terbutil-dimetil-sililo (1.1 equivalentes) y dimetil-amino-piridina (0.1 equivalentes) en dicloro-metano en una concentración de 0.1 M, se agitó durante 18 horas, en cuyo tiempo, los volátiles se removieron al vacío. La purificación directa del material crudo mediante cromatografía en columna (20

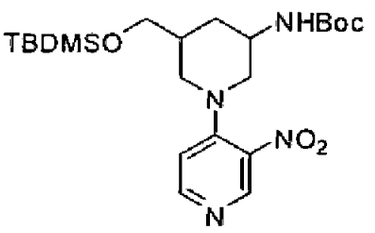
por ciento de acetato de etilo/hexanos) proporcionó el cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-1-carboxilato de bencilo. LCMS (*m/z*): 379.0 ($MH\text{-}Boc^+$); LC R_t = 5.95 minutos.

Síntesis de cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-3-il-carbamato de terbutilo



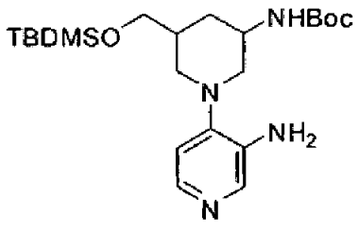
Se siguió el Método 2 para desproteger el cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-1-carboxilato de bencilo, proporcionando el cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 344.1 (MH^+).

Síntesis de cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



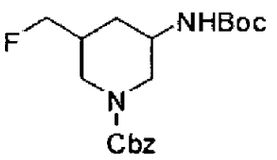
Se siguió el Método 1 utilizando el cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-3-il-carbamato de terbutilo y 4-cloro-3-nitro-piridina, proporcionando el cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 467.0 (MH^+); LC R_t = 4.02 minutos.

Síntesis de cis-(+/-)-1-(3-amino-piridin-4-il)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-3-il-carbamato de terbutilo



Siguiendo el Método 2, el cis-(+/-)-5-((terbutil-dimetil-sililoxi)-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo, proporcionando el cis-(+/-)-1-(3-amino-piridin-4-il)-5-((terbutil-dimetil-sililoxi)-metil)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 437.2 (MH^+); LC R_t = 3.86 minutos.

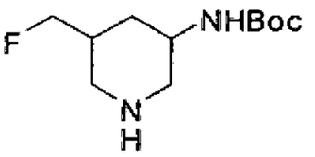
Síntesis de cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(fluoro-metil)-piperidin-1-carboxilato de bencilo



Una solución del cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(hidroxi-metil)-piperidin-1-carboxilato de bencilo (1 equivalente), fluoruro de perfluoro-butan-sulfonilo (2 equivalentes), trietil-amina-HF (4 equivalentes) y trietil-amina (6 equivalentes) en tetrahidrofurano, en una concentración de 0.16 M, se agitó durante 36 horas. Después de la dilución con acetato de etilo (50 veces), la solución se lavó con HCl 1N, $NaHCO_3$ saturado, y salmuera, se secó sobre $MgSO_4$, se filtró, se concentró, y se purificó mediante cromatografía en columna (del 25 al 40 por ciento de acetato de

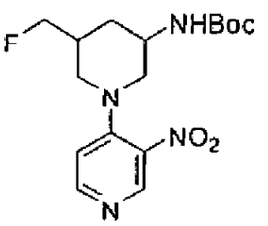
etilo/hexanos), para proporcionar el cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(fluoro-metil)-piperidin-1-carboxilato de bencilo (45 por ciento de rendimiento). LCMS (*m/z*): 267.1 (MH^+); LC R_t = 4.23 minutos.

Síntesis de cis-(+/-)-5-(fluoro-metil)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 2 para desproteger el cis-(+/-)-3-(terbutoxi-carbonil-amino)-5-(fluoro-metil)-piperidin-1-carboxilato de bencilo, proporcionando el cis-(+/-)-5-(fluoro-metil)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 233.1 (MH^+).

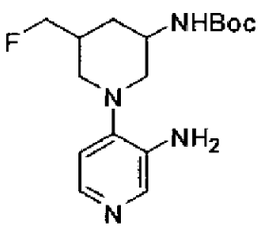
Síntesis de cis-(+/-)-5-(fluoro-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



Se siguió el Método 1 del Ejemplo 1, utilizando el cis-(+/-)-5-(fluoro-metil)-piperidin-3-il-carbamato de terbutilo y 4-cloro-3-nitro-piridina, proporcionando el cis-(+/-)-5-(fluoro-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo . LCMS (*m/z*): 355.1 (MH^+); LC R_t = 2.41 minutos.

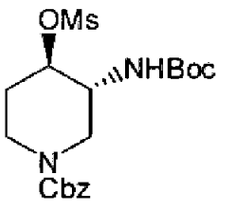
Síntesis de cis-(+/-)-1-(3-amino-piridin-4-il)-5-(fluoro-metil)-piperidin-

3-il-carbamato de terbutilo



Siguiendo el Método 2, el cis-(+/-)-5-(fluoro-metil)-1-(3-nitro-piridin-4-il)-piperidin-3-il-carbamato de terbutilo se redujo, proporcionando el cis-(+/-)-1-(3-amino-piridin-4-il)-5-(fluoro-metil)-piperidin-3-il-carbamato de terbutilo. LCMS (*m/z*): 325.1 (MH^+); LC R_t = 2.27 minutos.

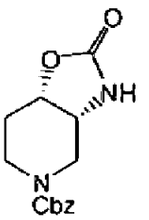
Síntesis de (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(metil-sulfoniloxi)-piperidin-1-carboxilato de bencilo



A una solución del (3R,4R)-3-(terbutoxi-carbonil-amino)-4-hidroxi-piperidin-1-carboxilato de bencilo en dicloro-metano (0.13 M), se le agregó trietil-amina (1.5 equivalentes), seguida por cloruro de metan-sulfonilo (1.3 equivalentes). La reacción se dejó agitándose a temperatura ambiente durante 15 horas. La solución entonces se apagó con $NaHCO_3$ saturado, se extrajo con dicloro-metano, se secó con sulfato de sodio, y se concentró, para dar el (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(metil-sulfoniloxi)-piperidin-1-carboxilato de bencilo crudo en un >95 por ciento de rendimiento. LCMS (*m/z*):

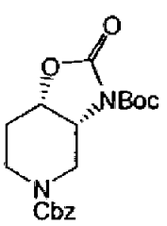
428.9/328.9 (MH^+), R_t = 3.81 minutos.

Síntesis de (3aR,7aS)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-5(6H)-carboxilato de bencilo



Una solución del (3R,4R)-3-(terbutoxi-carbonil-amino)-4-(metil-sulfoniloxi)-piperidin-1-carboxilato de bencilo en piridina (0.16 M) se calentó a 120°C en el reactor de microondas durante 10 minutos. La solución se concentró entonces hasta casi la sequedad, y el sólido formado se filtró, para dar el producto deseado. El filtrado se purificó adicionalmente mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo (100 por ciento), para proporcionar el (3aR,7aS)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-5(6H)-carboxilato de bencilo en un rendimiento combinado del 75 por ciento. LCMS (*m/z*): 277.1 (MH^+), R_t = 2.327 minutos.

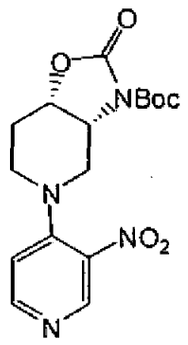
Síntesis de (3aR,7aS)-3-terbutil-2-oxo-tetrahidro-oxazolo-[4,5-c]-piridin-3,5(2H,6H)-dicarboxilato de 5-bencilo



A una solución del (3aR,7aS)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-5(6H)-carboxilato de bencilo (1.0 equivalentes) en dicloro-

metano (0.09 M), se le agregaron BOC_2O (1.1 equivalentes), trietil-amina (1.1 equivalentes), y una cantidad catalítica de DMAP. La reacción se agitó a temperatura ambiente durante una hora, en cuyo punto, se concentró al vacío y se filtró a través de un tapón de gel de sílice, eluyendo con acetato de etilo. El producto se secó al vacío para proporcionar el (3aR,7aS)-3-terbutil-2-oxo-tetrahidro-oxazolo-[4,5-c]-piridin-3,5(2H,6H)-dicarboxilato de 5-bencilo como un sólido blanco en un rendimiento del 75 por ciento. LCMS (*m/z*): 277.2 (MH^+), R_t = 3.43 minutos.

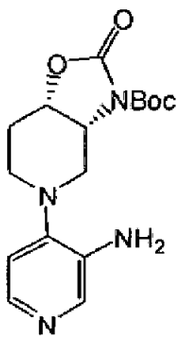
Síntesis de (3aR,7aS)-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo



A una solución del (3aR,7aS)-3-terbutil-2-oxo-tetrahidro-oxazolo-[4,5-c]-piridin-3,5(2H,6H)-dicarboxilato de 5-bencilo en una mezcla de EtOH y EtOAc (1 :1, 0.07 M), se le agregó Pd/C (al 10 por ciento en peso), y la reacción se agitó bajo un globo de hidrógeno durante 15 horas. La solución entonces se filtró a través de un cojín de Celite, y el filtrado se concentró a sequedad, para dar un aceite transparente. A una solución del (3aR,7aS)-terbutilo 2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato en i-PrOH (0.12

M), se le agregaron 4-cloro-3-nitro-piridina (1.2 equivalentes) y DIEA (4.0 equivalentes). La reacción se calentó a 75°C durante 2 horas, entonces se enfrió a temperatura ambiente, y se concentró al vacio. La mezcla cruda se diluyó con EtOAc, se agregó agua, la capa orgánica se extrajo, se lavó con salmuera, se secó con Na_2SO_4, y se concentró. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con EtOAc (100 por ciento), para proporcionar el (3aR,7aS)-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo como una espuma amarilla, en un rendimiento del 89 por ciento. LCMS (*m/z*): 365.1 (MH^+), R_t = 1.79 minutos.

Síntesis de (3aR,7aS)-5-(3-amino-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo

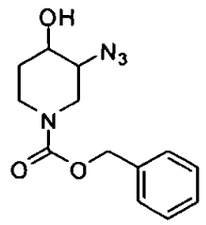


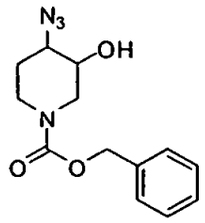
A una solución del (3aR,7aS)-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo en EtOH y EtOAc (1:1, 0.15 M), se le agregó Pd/C (al 10 por ciento en peso), y la reacción se agitó bajo un globo de hidrógeno durante 15 horas. La solución se filtró a través de un cojín de Celite, y el filtrado se concentró para proporcionar el (3aR,7aS)-5-(3-amino-piridin-4-il)-

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2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo como un aceite transparente en un >95 por ciento de rendimiento. LCMS (*m/z*): 335.0 (MH^+), R_t = 1.68 minutos.

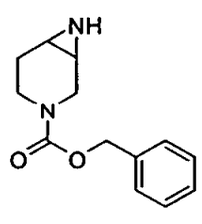
Síntesis de 3-azido-4-hidroxi-piperidin-1-carboxilato de bencilo y 4-azido-3-hidroxi-piperidin-1-carboxilato de bencilo





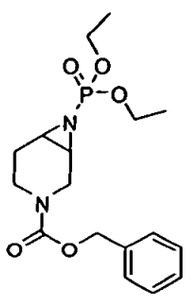
A una solución del 7-oxa-3-azabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo (1.0 equivalentes) en metanol y agua (0.17M), se le agregaron azida de sodio (2.0 equivalentes) y cloruro de amonio (1.0 equivalentes). La reacción se agitó a 65°C en un baño de aceite durante 7 horas, entonces se concentró para remover el metanol. Se agregó acetato de etilo, la fase orgánica se separó, se secó con Na_2SO_4, y se concentró al vacío, para dar el 3-azido-4-hidroxi-piperidin-1-carboxilato de bencilo y el 4-azido-3-hidroxi-piperidin-1-carboxilato de bencilo como un aceite transparente en un >95 por ciento de rendimiento. LCMS (*m/z*): 276.9 (MH^+), R_t = 2.98 minutos.

Síntesis de 3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo



A una solución del 3-azido-4-hidroxi-piperidin-1-carboxilato de bencilo y 4-azido-3-hidroxi-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en dioxano (0.14M), se le agregó PPh_3 (2.0 equivalentes), y la reacción se calentó a reflujo durante 1 hora. La solución se concentró entonces al vacío, y se purificó mediante cromatografía en columna de gel de sílice, eluyendo con dicloro-metano, MeOH al 10 por ciento, y Et_3N al 1 por ciento, para dar el 3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo como un aceite transparente en un 25 por ciento de rendimiento. LCMS (*m/z*): 233.0 (MH^+), R_t = 1.94 minutos.

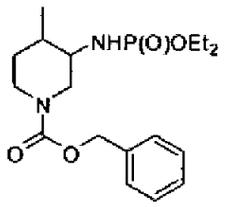
Síntesis de 7-(dietoxi-fosforil)-3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo



A una solución del 3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo (1.0 equivalentes) en dicloro-metano (0.26M), se le agregó fosforocloridato de dietilo (1.3 equivalentes) y trietil-amina (1.5 equivalentes). La reacción se agitó durante 24 horas, y entonces se concentró a sequedad. Se agregaron agua y acetato de etilo, los orgánicos se extrajeron, se secaron con Na_2SO_4, y se concentraron. El producto crudo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (del 50 por

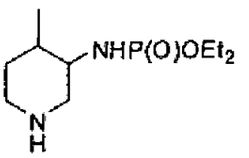
ciento al 100 por ciento de acetato de etilo), para proporcionar el 7-(dietoxi-fosforil)-3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo como un aceite transparente en un 21 por ciento de rendimiento. LCMS (*m/z*): 369.0 (MH^+).

Síntesis de 3-(dietoxi-fosforil-amino)-4-metil-piperidin-1-carboxilato de bencilo



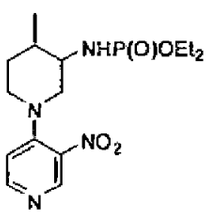
A una suspensión de CuI (0.3 equivalentes) en tetrahidrofurano anhidro (0.1M), se le agregó bromuro de metil-magnesio (solución 3M en Et_2O, 10 equivalentes) a –40°C. La reacción se agitó durante 30 minutos, seguido por la adición del 7-(dietoxi-fosforil)-3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo (1.0 equivalentes) en tetrahidrofurano (0.1M) a –40°C. La reacción se dejó calentar a 10°C durante 5 horas, entonces se apagó con agua, y se extrajo con acetato de etilo. La fase orgánica se concentró al vacío, y se purificó mediante cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y hexanos (del 50 por ciento al 100 por ciento de acetato de etilo), para proporcionar el 3-(dietoxi-fosforil-amino)-4-metil-piperidin-1-carboxilato de bencilo en un 35 por ciento de rendimiento. LCMS (*m/z*): 385.0 (MH^+), R_t = 3.38 minutos.

Síntesis de 4-metil-piperidin-3-il-fosforamidato de dietilo



A una solución del 3-(dietoxi-fosforil-amino)-4-metil-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en metanol desgasificado, se le agregó Pd/C (al 10 por ciento en peso), y la reacción se agitó bajo una atmósfera de hidrógeno durante 1 hora. La solución se filtró, y entonces se concentró para proporcionar el 4-metil-piperidin-3-il-fosforamidato de dietilo en un 83 por ciento de rendimiento. LCMS (*m/z*): 251.1 (MH^+).

Síntesis de 4-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo

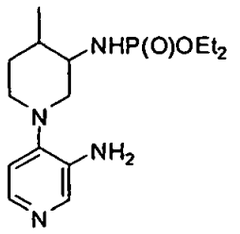


A una solución del 4-metil-piperidin-3-il-fosforamidato de dietilo (1.0 equivalentes) en alcohol isopropílico, se le agregó 4-cloro-3-nitro-piridina (2.0 equivalentes) y DIEA (1.1 equivalentes). La reacción se calentó a 70°C durante 18 horas, entonces se apagó con agua, y se extrajo con acetato de etilo. Los orgánicos se secaron y se concentraron al vacío. El producto crudo se purificó por medio de ISCO (acetato de etilo y hexanos), para proporcionar el 4-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo en un 52 por

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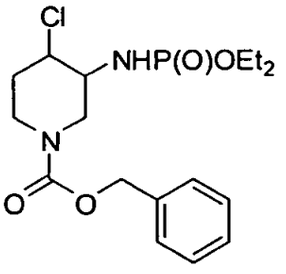
ciento de rendimiento. LCMS (*m/z*): 373.0 (MH^+), R_t = 1.93 minutos.

Síntesis de 1-(3-amino-piridin-4-il)-4-metil-piperidin-3-il-fosforamidato de dietilo



A una solución del 4-metil-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo (1.0 equivalentes) en EtOAc desgasificado (0.1M), se le agregó Pd/C (al 10 por ciento en peso), y la reacción se agitó bajo una atmósfera de hidrógeno durante 18 horas. Se filtró, y el filtrado se concentró, para proporcionar el 1-(3-amino-piridin-4-il)-4-metil-piperidin-3-il-fosforamidato de dietilo en un 86 por ciento de rendimiento. LCMS (*m/z*): 343.0 (MH^+), R_t = 1.85 minutos.

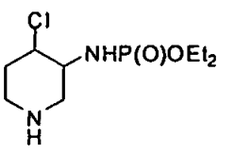
Síntesis de 4-cloro-3-(dietoxi-fosforil-amino)-piperidin-1-carboxilato de bencilo



A una solución del 7-(dietoxi-fosforil)-3,7-diazabiciclo-[4.1.0]-heptan-3-carboxilato de bencilo (1.0 equivalentes) y clorhidrato de trietil-amina (4 equivalentes) en dicloro-metano (0.1M), se le agregó $BF_3.OEt_2$ (2.0 equivalentes), y la reacción se dejó agitándose a

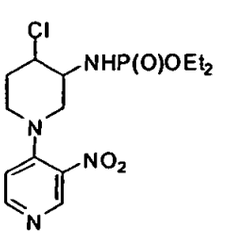
temperatura ambiente durante 2 horas bajo una atmósfera de nitrógeno. La solución entonces se apagó con agua, y se extrajo con dicloro-metano. El producto crudo se purificó mediante cromatografía en columna de gel de sílice (ISCO eluyendo con EtOAc y hexanos, del 50 por ciento al 100 por ciento de EtOAc), para proporcionar el 4-cloro-3-(dietoxi-fosforil-amino)-piperidin-1-carboxilato de bencilo en un rendimiento del 89 por ciento. LCMS (*m/z*): 405.1 (MH^+), R_t = 2.73 minutos.

Síntesis de 4-cloro-piperidin-3-il-fosforamidato de dietilo



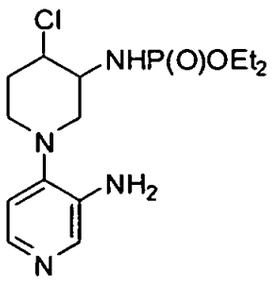
A una solución del 4-cloro-3-(dietoxi-fosforil-amino)-piperidin-1-carboxilato de bencilo (1.0 equivalentes) en metanol desgasificado se le agregó Pd/C (al 10 por ciento en peso), y la reacción se agitó bajo una atmósfera de hidrógeno durante 1 hora. La solución se filtró, y entonces se concentró, para proporcionar el 4-cloro-piperidin-3-il-fosforamidato de dietilo en un 92 por ciento de rendimiento. LCMS (*m/z*): 271.0 (MH^+).

Síntesis de 4-cloro-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo



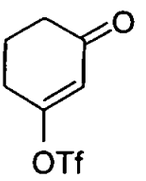
A una solución de 4-cloro-piperidin-3-il-fosforamidato de dietilo (1.0 equivalentes) en alcohol isopropílico (0.1M), se le agregó 4-cloro-3-nitro-piridina (2.0 equivalentes) y DIEA (1.1 equivalentes). La reacción se calentó a 70°C durante 18 horas, entonces se apagó con agua y se extrajo con acetato de etilo. Los orgánicos se secaron y se concentraron al vacío. El producto crudo se purificó por medio de ISCO (acetato de etilo y hexanos, y luego metanol al 10 por ciento en dicloro-metano), para proporcionar el 4-cloro-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo en un 69 por ciento de rendimiento. LCMS (*m/z*): 393.1 (MH^+), R_t = 2.01 minutos.

Síntesis de 1-(3-amino-piridin-4-il)-4-cloro-piperidin-3-il-fosforamidato de dietilo



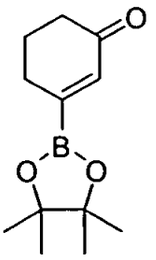
A una solución de 4-cloro-1-(3-nitro-piridin-4-il)-piperidin-3-il-fosforamidato de dietilo (1.0 equivalentes) en EtOAc desgasificado (0.1M), se le agregó Pd/C (al 10 por ciento en peso) y la reacción se agitó bajo una atmósfera de hidrógeno durante 18 horas. Se filtró, y el filtrado se concentró para proporcionar el 1-(3-amino-piridin-4-il)-4-cloro-piperidin-3-il-fosforamidato de dietilo en un 83 por ciento de rendimiento. LCMS (*m/z*): 363.1 (MH^+), R_t = 1.89 minutos.

Síntesis de trifluoro-metan-sulfonato de 3-oxociclohex-1-enilo



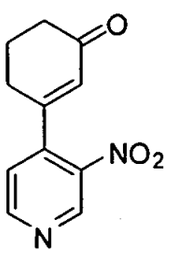
A una solución de ciclohexano-1,3-diona (1 equivalente) en dicloro-metano (0.4M), se le agregó Na_2CO_3 (1.0 equivalentes) y se enfrió a 0°C. Se le agregó Tf_2O (1.0 equivalentes) en dicloro-metano (5M) por goteo durante 1 hora a temperatura ambiente bajo una atmósfera de nitrógeno. Después de la adición, 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 producto crudo se purificó por medio de cromatografía en columna con SiO_2 eluyendo con dicloro-metano y hexanos (1:1) o de una manera alternativa por medio de un tapón de aluminio neutro eluyendo con dicloro-metano, para proporcionar el trifluoro-metan-sulfonato de 3-oxociclohex-1-enilo en 30 por ciento o 67 por ciento de rendimiento, respectivamente. 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).

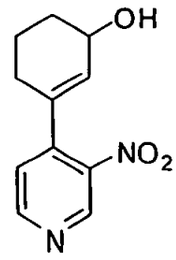
Síntesis de 3-(3-nitro-piridin-4-il)-ciclohex-2-enona



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 $Pd(PPh_3)_4$ (0.05 equivalentes). La reacción se calentó en un baño de aceite a 120°C durante 30 minutos. (La reacción también se puede llevar a cabo en el reactor de microondas durante 10 minutos a 120°C). Se enfrió a temperatura ambiente, entonces se

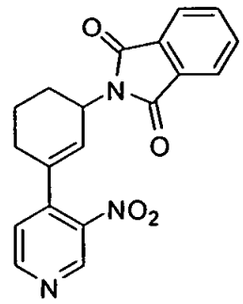
diluyó con EtOAc, se le agregaron varias emulsiones de H_2O – solución oscura. Se filtró para dar la liberación de los sólidos, entonces se extrajo la fase orgánica, se secó con Na_2SO_4, y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice, para proporcionar la 3-(3-nitro-piridin-4-il)-ciclohex-2-enona (64 por ciento, 2 pasos). LC/MS = 219 (M+H), LC = 2.29 minutos.

Síntesis de 3-(3-nitro-piridin-4-il)-ciclohex-2-enol



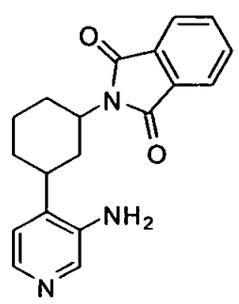
A una solución de la 3-(3-nitro-piridin-4-il)-ciclohex-2-enona (1.0 equivalentes), se le agregaron EtOH (1.1 M) y $CeCl_3$-$7H_2O$ (1.3 equivalentes). La reacción se enfrió a 0°C, y entonces se le agregó en porciones $NaBH_4$ (1.3 equivalentes). Se agitó durante 2 horas a 0°C, entonces se apagó mediante 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 = 2.24 minutos.

Síntesis de 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolin-1,3-diona



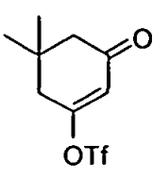
A una solución homogénea de 3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes), trifenil-fosfina (1.5 equivalentes), y ftalimida (1.5 equivalentes) en tetrahidrofurano (0.2 M) enfriada a 0°C, se le agregó azodicarboxilato de diterbutilo (1.5 equivalentes) en tetrahidrofurano. La mezcla se agitó 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 un sólido, el cual además se trituró con dicloro-metano y hexanos, para proporcionar el producto crudo, más el filtrado. La purificación adicional del filtrado proporcionó más producto crudo. El rendimiento total de la 2-(3-(3-nitro-piridin-4-il)-ciclohex-2-enil)-isoindolin-1,3-diona es del 58 por ciento. LC/MS (*m/z*): MH^+=350.2, Rt=0.96. HPLC Rt=3.73.

Síntesis de 2-(3-(3-amino-piridin-4-il)-ciclohexil)-isoindolin-1,3-diona



Una solución de la 2-(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 le agregó Pd/C al 10 por ciento (0.15 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante cuatro días bajo una atmósfera de hidrógeno. Los sólidos se removieron mediante filtración sobre Celite, entonces se enjuagaron con EtOAc y metanol. El filtrado se concentró, se diluyó con EtOAc, y se lavó dos veces con Na_2CO_3 2M acuoso saturado. La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró. Se trituró a partir de EtOAc/hexanos, para dar la 2-(3-(3-amino-pirin-4-il)-ciclohexil)-isoindolin-1,3-diona en un 77 por ciento de rendimiento. LC/MS (*m/z*): MH^+=322.2, Rt=0.64. HPLC Rt=2.43 minutos.

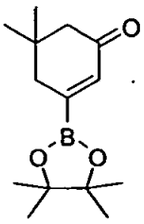
Síntesis de trifluoro-metan-sulfonato de 5,5-dimetil-3-oxociclohex-1-enilo



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 ^{1}H 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.

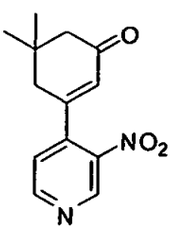
Síntesis de 5,5-dimetil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona



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 aducto de $PdCl_2$(dppf) –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.

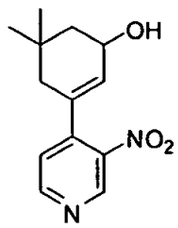
Síntesis de 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona



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. A la mezcla se le agregó EtOAc y agua. La mezcla resultante se filtró a través de Celite, y la torta se lavó con EtOAc. La capa orgánica se separó. La fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se

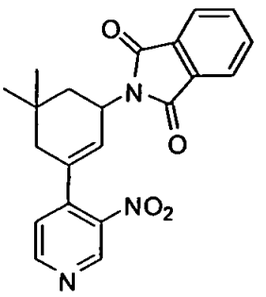
secaron sobre $MgSO_4$, y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (eluido con EtOAc:Hexanos = 1:10 a 2:1), para dar la 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (46.7 por ciento en tres pasos). LC/MS (*m/z*): MH^+=247.2, Rt=0.79 minutos.

Síntesis de 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol



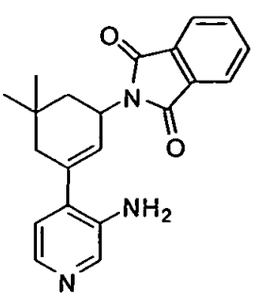
A una solución de la 5,5-dimetil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona (1.0 equivalentes), y $CeCl_3$-$7H_2O$ (1.2 equivalentes) en metanol (0.2 M), se le agregó $NaBH_4$ (1.0 equivalentes) a 0°C. La solución se agitó durante 1 hora, y entonces se apagó con 5 mililitros de agua. Los volátiles se 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, Rt=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.

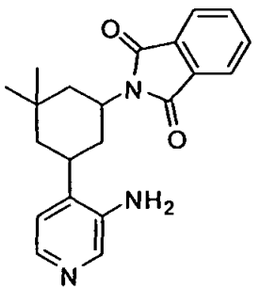
<u>Síntesis de 2-(3-(3-amino-piridin-4-il)-5,5-dimetil-ciclohex-2-enil)-isoindolin-1,3-diona</u>



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.

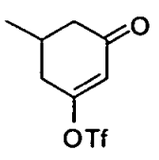
Síntesis de 2-(5-(3-amino-piridin-4-il)-3,3-dimetil-ciclohexil)-isoindolin-1,3-diona



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 300 psi (21.1 kg/cm^2) en una bomba de acero durante la noche, y a 65°C, a 300 psi (21.1 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 = 7.53 minutos y 13.11 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). ^{1}H 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).

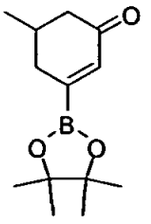
<u>Síntesis de trifluoro-metan-sulfonato de 5-metil-3-oxociclohex-1-enilo</u>



A una solución de 5-metil-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 agregó Tf_2O (1.0 equivalentes) en dicloro-metano

(5M) por goteo durante 1 hora a 0°C bajo una atmósfera de nitrógeno. Después de la adición, la reacción se agitó durante 2 horas a temperatura ambiente (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 con Na_2SO_4, y se concentraron. El producto crudo se purificó por medio de cromatografía en columna con SiO_2 eluyendo con dicloro-metano y hexanos (1:1), o de una manera alternativa, por medio de un tapón de alúmina neutra eluyendo con dicloro-metano, para proporcionar trifluoro-metan-sulfonato de 5-metil-3-oxociclohex-1-enilo en un 30 por ciento o en un 67 por ciento de rendimiento, respectivamente. El triflato se descompone debido al almacenamiento y debería utilizarse inmediatamente para la siguiente reacción. LC/MS=259.1/300.1 (M+H y M+CH_3CN); Rt = 0.94 minutos, LC = 3.84 minutos.

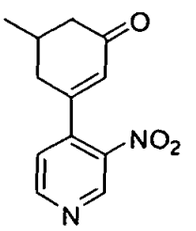
Síntesis de 5-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona



A una solución del trifluoro-metan-sulfonato de 5-metil-3-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

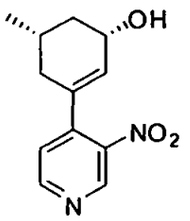
reacción se calentó a 80°C durante 10 horas, y entonces se filtró. La solución de dioxano se utilizó para el siguiente paso sin mayor purificación. LC/MS = 155.1 (M+H de ácido borónico); Rt = 0.41 minutos, LC = 1.37 minutos.

Síntesis de 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona



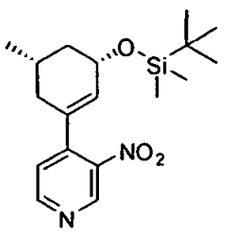
A una solución de la 5-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-ciclohex-2-enona (1.0 equivalentes) en dioxano desgasificado y Na_2CO_3 2M, se le agregaron 4-cloro-3-nitro-piridina (1.2 equivalentes) y $Pd(PPh_3)_4$ (0.05 equivalentes). La reacción se calentó en un baño de aceite a 120°C durante 2 horas. (La reacción también se puede llevar a cabo en el reactor de microondas durante 10 minutos a 120°C). Se enfrió a temperatura ambiente, entonces se diluyó con EtOAc, se agregó H_2O – solución oscura, gran cantidad de emulsiones. Se filtró para deshacerse 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, para proporcionar la 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enona. LC/MS = 233.2 (M+H); Rt = 0.69 minutos, LC = 2.70 minutos.

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), se le agregaron EtOH (1.1 M) y $CeCl_3$-$7H_2O$ (1.3 equivalentes). La reacción se enfrió a 0°C, y entonces se 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 secó con salmuera, luego con Na_2SO_4, y se concentró, para proporcionar el 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (91 por ciento). LC/MS = 235.2.(M+H), LC = 2.62 minutos.

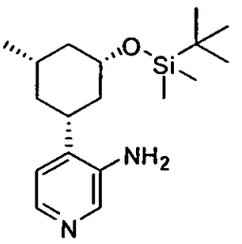
Síntesis de cis-(+/-)-4-(3-(terbutil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina



A una solución de 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en N,N-dimetil-formamida (0.5 M), se le agregaron imidazol (4.0 equivalentes) y TBDSMCl (2.5 equivalentes). Después de agitar durante 18 horas, la solución se dividió entre EtOAc y H_2O, y se separó. Después de lavar adicionalmente con H_2O (3 veces) y NaCl saturado, de secar sobre $MgSO_4$, de filtrar, y de remover los

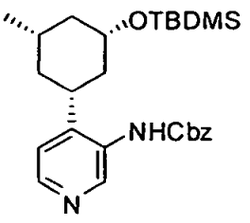
solventes, se obtuvo la 4-(3-(terbutil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (85 por ciento). LC/MS = 349.2 (M+H), LC = 5.99 minutos.

Síntesis de cis-(+/-)-4-(3-(terbutil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina



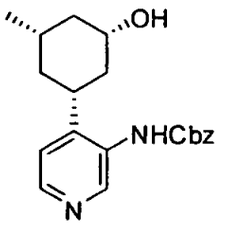
A una solución de la cis--(terbutil-dimetil-sililoxi)-5-metil-ciclohex-1-enil)-3-nitro-piridina (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó paladio al 10 por ciento sobre carbón (0.1 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 15 horas. En este tiempo, la mezcla se filtró a través de un cojín de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando toda la cis-4-(3-(terbutil-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-(terbutil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo



A una solución de la cis-(+/-)-4-(3-(terbutil-dimetil-sililoxi)-5-metil-ciclohexil)-piridin-3-amina en dicloro-metano en una concentración de 0.5M, se le agregaron 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, del secado sobre $MgSO_4$, de la filtración y la remoción de los solventes, se obtuvo el cis-(+/-)-4-3-(terbutil-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.

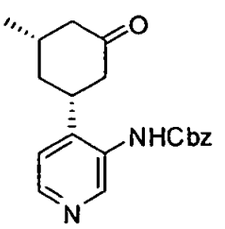
<u>Síntesis de cis-(+/-)-4-(3-hidroxi-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo</u>



Una solución del cis-(+/-)-4-3-(terbutil-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 fase 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-oxociclohexil)-piridin-3-il-carbamato de bencilo

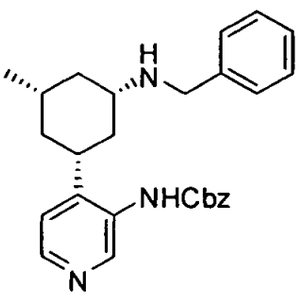


A una solución a 0°C del cis-(+/-)-4-(3-hidroxi-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo en CH_2Cl_2 húmedo, en una concentración de 0.16 M, se le agregó peryodinano Dess-Martin (1.5 equivalentes), y la solución se agitó durante 18 horas a medida que se calentaba a temperatura ambiente. La solución se dividió entre EtOAc y 1:1 de $Na_2S_2O_3$ al 10 por ciento / $NaHCO_3$ saturado, y se separó. Después de un lavado adicional con 1:1 de $Na_2S_2O_3$ al 10 por ciento / $NaHCO_3$ saturado (2 veces) y NaCl saturado, del secado sobre $MgSO_4$, de la filtración, de la remoción de los solventes, y de la purificación mediante cromatografía en gel de sílice (del 75 al 100

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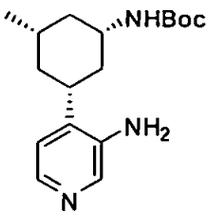
por ciento de EtOAc/hexanos), se obtuvo el cis-(+/-)-4-(3-metil-5-oxociclohexil)-piridin-3-il-carbamato de bencilo como un sólido blanco (53 por ciento, 5 pasos). LC/MS = 339.2 (M+H).

Síntesis de cis-(+/-)-4-(-3-(bencil-amino)-5-metil-ciclohexil)-piridin-3-il-carbamato de bencilo



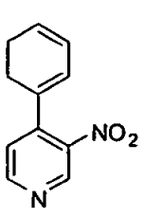
Una solución del cis-(+/-)-4-(3-metil-5-oxociclohexil)-piridin-3-il-carbamato de bencilo (1.0 equivalentes) y bencil-amina (3.0 equivalentes) en MeOH, en una concentración de 0.25 M, se agitó a temperatura ambiente durante 2 horas. Después de enfriarse en un baño a -78°C, se agregó $LiBH_4$ (1.1 equivalentes, 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, 4:1, con todos los *cis* como predominantes, LC/MS = 430.3 (M+H), LC = 0.62 minutos.

Síntesis de cis-(+/-)-(-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo



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 un cojín de Celite, eluyendo con metanol. Después de la remoción de los volátiles al vacío, de la purificación mediante cromatografía en gel de sílice (2.5-2.5 de $MeOH/CH_2Cl_2$ con DIEA al 0.1 por ciento), y de la recristalización a partir de EtOAc al 10 por ciento/hexanos, proporcionó el cis-(+/-)-(-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo (49 por ciento). LCMS (*m/z*): 306.3 (MH^+), LC R_t = 2.59 minutos. Se pudieron obtener los enantiómeros puros mediante cromatografía quiral.

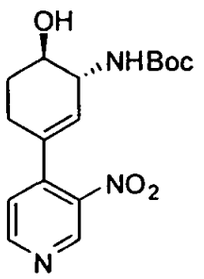
Síntesis de 4-(ciclohexa-1,3-dienil)-3-nitro-piridina



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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).

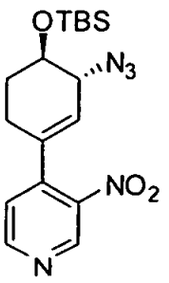
Síntesis de 6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo



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 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 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 6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo (82 por ciento). LC/MS (*m/z*): MH^+=336.0, Rt=0.71

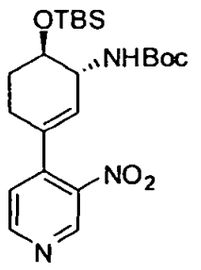
Síntesis de (+/-)-4-(3-azido-4-(terbutil-dimetil-sililoxi)-ciclohex-1-enil)-3-nitro-piridina



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 ISCO eluyendo con acetato de etilo y hexanos (20 por ciento). Se obtuvo la (+/-)-4-(3-azido-4-(terbutil-

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.

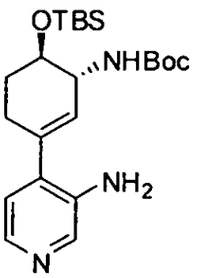
Síntesis de (+/-)-6-(terbutil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo



En un matraz de fondo redondo se agregaron (+/-)-4-(3-azido-4-(terbutil-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 ISCO (5:1 de Hex/EtOAc). Las fracciones recolectadas puras se concentraron, para dar el (+/-)-6-(terbutil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo como una espuma. LCMS

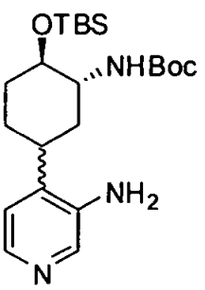
(*m/z*): 450.3 (MH^+), LC R_t = 5.83 minutos.

Síntesis de (+/-)-3-(3-amino-piridin-4-il)-6-(terbutil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de terbutilo



A una solución del (+/-)-6-(terbutil-dimetil-sililoxi)-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo (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-(terbutil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de terbutilo 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-(terbutil-dimetil-sililoxi)-ciclohexil-carbamato de terbutilo

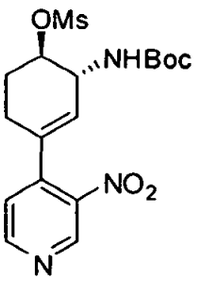


A una solución del (+/-)-3-(3-amino-piridin-4-il)-6-(terbutil-dimetil-sililoxi)-ciclohex-2-enil-carbamato de terbutilo (1.0 equivalentes) en metanol (0.1M), se le agregó Pd/C (al 20 por ciento en peso), y la reacción se agitó bajo un globo de hidrógeno durante 18 horas. La LC/MS de la reacción indicó 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.

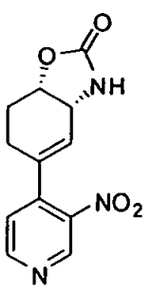
Síntesis de metan-sulfonato de 2-(terbutoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



A una solución del 6-hidroxi-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo (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

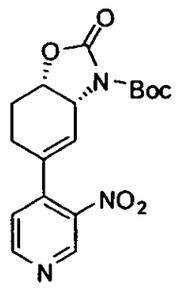
horas a esa temperatura. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con NaCl saturado. La fase orgánica se secó con $MgSO_4$, se filtró, y se concentró, para dar el metan-sulfonato de 2-(terbutoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (85 por ciento), el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+=414.0, Rt=0.82

Síntesis de (+/-)-5-(3-nitro-piridin-4-il)-3,3a,7,7a-tetrahidro-benzo-[d]-oxazol-2(6H)-ona



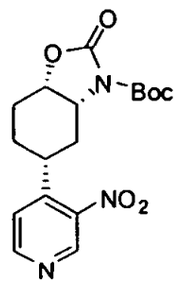
La mezcla de metan-sulfonato de 2-(terbutoxi-carbonil-amino)-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en piridina (0.21 M) se agitó a 110°C durante 10 minutos en microondas. La piridina se removió bajo presión reducida. El residuo se disolvió en acetato de etilo, y se lavó con NaCl 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

Síntesis de (+/-)-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo



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 terbutilo (98 por ciento). LC/MS (*m/z*): MH^+=306.0, Rt=0.75

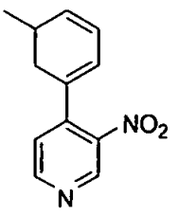
Síntesis de (+/-)-5-(3-amino-piridin-4-il)-2-oxohexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo



A una solución del 5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-

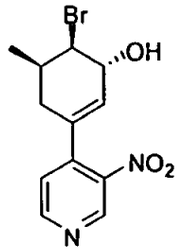
tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo (1.0 equivalentes) en metanol y acetato de etilo (1;1, 0.1 M), se le agregó Pd/C (al 10 por ciento). La mezcla resultante se agitó bajo una atmósfera de H_2 durante 6 horas. El sólido se removió mediante filtración. El filtrado se concentró bajo presión reducida, para dar el 5-(3-amino-piridin-4-il)-2-oxohexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo (87 por ciento), el cual se utilizó en el siguiente paso sin mayor purificación. LC/MS (*m/z*): MH^+=334.1, Rt=0.51.

Síntesis de (+/-)-4-(5-metil-ciclohexa-1,3-dienil)-3-nitro-piridina



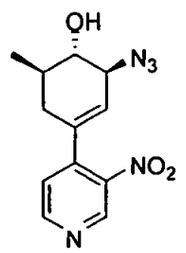
A una solución del 5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en dioxano (0.1M), se le agregó p-TSA (1.0 equivalentes), y la reacción se agitó a 100°C durante 3 horas. La solución se enfrió a temperatura ambiente, entonces se pasó a través de un cojín de alúmina neutra eluyendo 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 (+/-)-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, 0.13M), se le agregó NBS (1.5 equivalentes), y la reacción se agitó a temperatura ambiente durante 30 minutos. Al completarse, se agregaron acetato de etilo y agua a la reacción, 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.

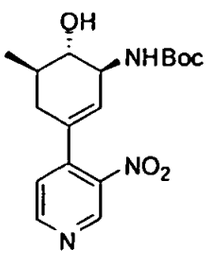
Síntesis de (+/-)-2-azido-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enol



A una solución del (+/-)-6-bromo-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enol (1.0 equivalentes) en tetrahidrofurano (0.1M), se le

agregó terbutóxido de potasio (1.5 equivalentes). La reacción cambió desde color naranja hasta negro casi inmediatamente. De acuerdo con la TLC, la formación de 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 con sulfato de sodio, se filtró, y se concentró. El producto crudo se disolvió en etanol y agua (3:1, 0.1M), 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, 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 silice, 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.

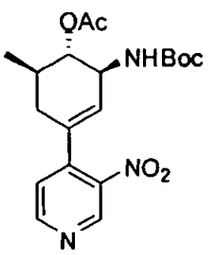
Síntesis de (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo



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 vacio. Se agregó más etanol, y la reacción se concentró nuevamente. Se agregaron dioxano y $NaHCO_3$ saturado (1:1, 0.08M) al producto crudo, seguidos por Boc_2O (1.0 equivalentes). Se agitó la mezcla de reacción a temperatura ambiente durante 2 horas, 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 terbutilo (59 por ciento). LC/MS = 350.1 (M+H), Rt: 0.76 minutos.

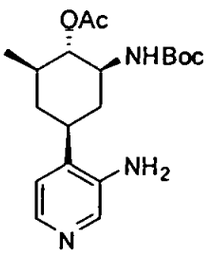
Síntesis de (+/-)-acetato de 2-(terbutoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



A una solución del (+/-)-6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo (1.0 equivalentes) en piridina (0.1M), 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-(terbutoxi-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.

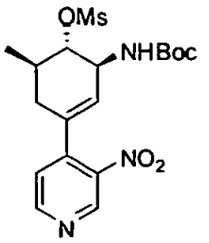
Síntesis de (+/-)-acetato de 4-(3-amino-piridin-4-il)-2-(terbutoxi-carbonil-amino)-6-metil-ciclohexilo



A una solución desgasificada de (+/-)-acetato de 2-(terbutoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en metanol y EtOAc (1:1, 0.1M), se le agregó Pd/C (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 un cojín de Celite, el cojín se lavó con acetato de etilo, y el filtrado se concentró. El material crudo contuvo aproximadamente el 10 por ciento del isómero indeseado. El producto crudo se disolvió en acetato de etilo (aproximadamente al 20 por ciento) y hexanos, y se calentó hasta que todo se disolvió. La solución se dejó asentarse a temperatura ambiente durante 2 días. El precipitado se recolectó entonces, para dar el (+/-)-acetato de 4-(3-

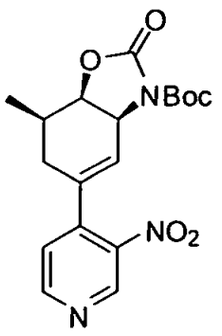
amino-piridin-4-il)-2-(terbutoxi-carbonil-amino)-6-metil-ciclohexilo como el producto puro en un 59 por ciento de rendimiento. LC/MS = 364.3 (M+H), Rt = 0.63 minutos.

Síntesis de metan-sulfonato de 2-(terbutoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo



A una solución de 6-hidroxi-5-metil-3-(3-nitro-piridin-4-il)-ciclohex-2-enil-carbamato de terbutilo (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. Se procesó la reacción 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-(terbutoxi-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.

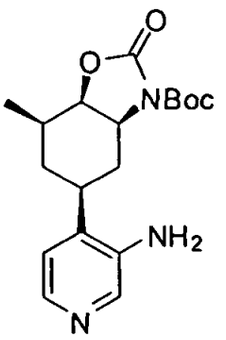
Síntesis de (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo



Una solución del (+/-)-metan-sulfonato de 2-(terbutoxi-carbonil-amino)-6-metil-4-(3-nitro-piridin-4-il)-ciclohex-3-enilo (1.0 equivalentes) en piridina (0.2M) se calentó en microondas a 110°C durante 10 minutos. La 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 (0.2M), 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 terbutilo como una espuma blanca en un 66 por ciento de rendimiento. LC/MS = 376.0 (M+H), LC: 3.424 minutos.

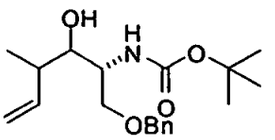
Síntesis de (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxohexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo

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A una solución desgasificada de (+/-)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-3a,6,7,7a-tetrahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo (1.0 equivalentes) en metanol y EtOAc (1:1, 0.1M), se le agregó Pd/C (0.1 equivalentes). La reacción se agitó bajo un globo de hidrógeno durante la noche. Al completarse, la solución se filtró a través de un cojín de Celite, y el cojín se lavó con acetato de etilo. El filtrado se concentró al vacío, para dar el (+/-)-5-(3-amino-piridin-4-il)-7-metil-2-oxohexahidro-benzo-[d]-oxazol-3(2H)-carboxilato de terbutilo como el producto deseado, como una espuma amarilla en un 93 por ciento de rendimiento. LC/MS = 348.1 (M+H), Rt = 055 minutos.

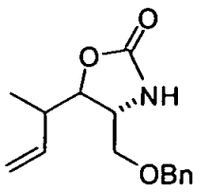
Síntesis de (2R)-1-(benciloxi)-3-hidroxi-4-metilhex-5-en-2-il-carbamato de terbutilo



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-

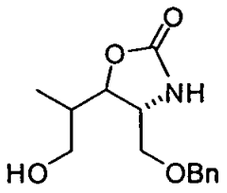
dioxaborolano (1.1 equivalentes), y la solución transparente se agitó durante 16 horas a medida que se calentaba a temperatura ambiente. La solución se agregó a EtOAc, y se lavó con H_2O (3 veces) y NaCl saturado, se secó sobre $MgSO_4$ y se purificó mediante cromatografía en gel de sílice (15 por ciento de EtOAc/hexanos), para proporcionar el (2R)-1-(benciloxi)-3-hidroxi-4-metilhex-5-en-2-il-carbamato de terbutilo (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-metilhex-5-en-2-carbamato de terbutilo 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.

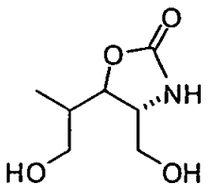
Síntesis de (4R)-4-(benciloxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona



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.

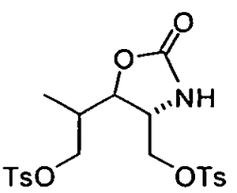
Síntesis de (4R)-4-(hidroxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-

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 un cojín 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^+).

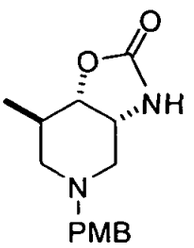
Síntesis de 4-metil-bencen-sulfonato de 2-((4R)-2-oxo-4-(tosiloxi-metil)-oxazolidin-5-il)-propilo

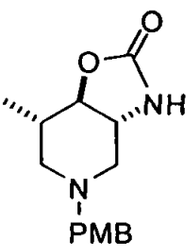


A una solución de la (4R)-4-(hidroxi-metil)-5-(1-hidroxi-propan-2-il)-oxazolidin-2-ona (1.0 equivalentes) en piridina (0.15 M) a 0°C, se le agregó cloruro de p-toluen-sulfonilo (2.1 equivalentes). La solución se dejó calentar a temperatura ambiente a medida que se agitaba durante 14 horas, en cuyo tiempo, 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.

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

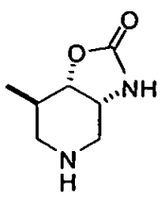




Una solución del 4-metil-bencen-sulfonato de 2-((4R)-2-oxo-4-(tosiloxi-metil)-oxazolidin-5-il)-propilo (1.0 equivalentes), di-isopropil-etil-amina (3.0 equivalentes), y para-metoxi-bencil-amina (1.5 equivalentes) en NMP (0.05 M) se calentó a 100°C durante 14 horas. La solución se purificó directamente 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

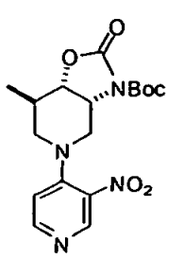
(3aR,7S,7aR)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (27 por ciento y 8 por ciento). LCMS (*m/z*): 277.2 (MH^+).

Síntesis de (3aR,7R,7aS)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona



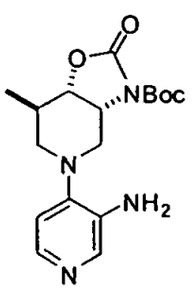
A una solución de la (3aR,7R,7aS)-5-(4-metoxi-bencil)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (1.0 equivalentes) en metanol, en una concentración de 0.1 M, se le agregó hidróxido de paladio al 20 por ciento sobre carbón (0.3 equivalentes). La solución heterogénea resultante se puso bajo una atmósfera de hidrógeno, y se agitó durante 2 horas. En este tiempo la mezcla se filtró a través de un cojin 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^+).

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 terbutilo



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 terbutilo (62 por ciento). LCMS (*m/z*): 379.0 (MH^+).

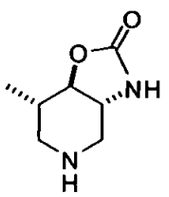
Síntesis de (3aR,7R,7aS)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo



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 terbutilo (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 un cojín 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 terbutilo. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.06 minutos.

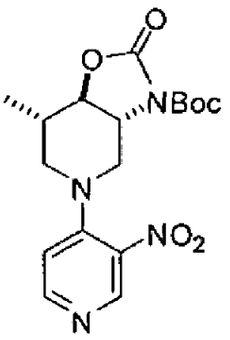
Síntesis de (3aR,7S,7aR)-7-metil-hexahidro-oxazolo-[4,5-c]-piridin-2(3H)-ona



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 un cojín de Celite, eluyendo con metanol. Los volátiles se removieron al vacío, proporcionando la (3aR,7S,7aR)-7-metil-hexa-hidro-oxazolo-[4,5-c]-piridin-2(3H)-ona (99 por ciento). LCMS (*m/z*): 157.1 (MH^+).

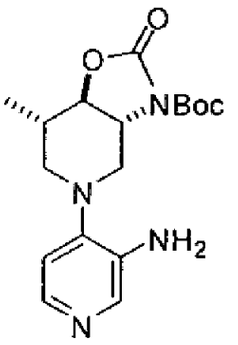
Síntesis de (3aR,7S,7aR)-7-metil-5-(3-nitro-piridin-4-il)-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo

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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 terbutilo (35 por ciento). LCMS (*m/z*): 379.0 (MH^+). LC R_t = 2.42 minutos.

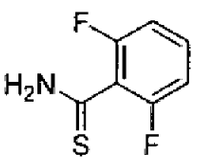
Síntesis de (3aR,7R,7aS)-5-(3-amino-piridin-4-il)-7-metil-2-oxo-hexahidro-oxazolo-[4,5-c]-piridin-3(2H)-carboxilato de terbutilo



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 terbutilo (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 un cojín 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 terbutilo. LCMS (*m/z*): 349.1 (MH^+); LC R_t = 2.18 minutos.

Método 3

Síntesis de 2,6-difluoro-benzotioamida

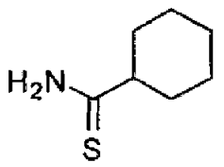


Una solución de 2,6-difluoro-benzamida (1 equivalente) y reactivo de Lawesson (0.5 equivalentes) en tolueno (0.2 M), se calentó a 90°C durante 14 horas. Después de enfriarse, los volátiles

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se removieron al vacío, y se purificaron mediante cromatografía con SiO_2 (25 por ciento de EtOAc/hexanos), proporcionando la 2,6-difluoro-benzotioamida como un sólido amarillo claro (99 por ciento). LCMS (*m/z*): 174.1 (MH^+); LC R_t = 2.19 minutos.

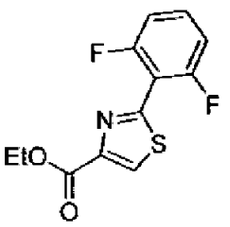
Síntesis de ciclohexan-carbotioamida



Siguiendo el Método 3, la ciclohexan-carboxamida y el reactivo de Lawesson se hicieron reaccionar, proporcionando la ciclohexan-carbotioamida. LCMS (*m/z*): 144.1 (MH^+); LC R_t = 5.10 minutos.

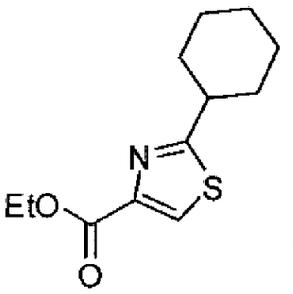
Método 4

Síntesis de 2-(2,6-difluoro-fenil)-tiazol-4-carboxilato de etilo



Una solución de 2,6-difluoro-benzotioamida (1.0 equivalentes) y bromo-piruvato de etilo (1.0 equivalentes) en etanol (1.0 M), s calentó en microondas a 130°C durante 30 minutos. Después de la remoción de los volátiles al vacío, se agregó acetato de etilo, y la solución se lavó con Na_2CO_3 saturado, con NaCl saturado, se secó sobre $MgSO_4$, se filtró, y se concentró, proporcionando el 2-(2,6-difluoro-fenil)-tiazol-4-carboxilato de etilo (84 por ciento). LCMS (*m/z*): 270.1 (MH^+); LC R_t = 3.79 minutos.

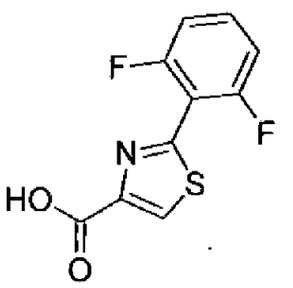
Síntesis de 2-ciclohexil-tiazol-4-carboxilato de etilo



Siguiendo el Método 4, se utilizó ciclohexan-carbotioamida para proporcionar el 2-ciclohexil-tiazol-4-carboxilato de etilo. LCMS (*m/z*): 240.1 (MH^+); LC R_t = 3.90 minutos.

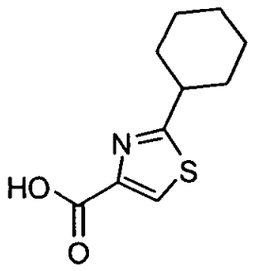
Método 5

Síntesis de ácido 2-(2,6-difluoro-fenil)-tiazol-4-carboxílico



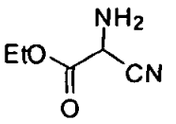
A una solución del 2-(2,6-difluoro-fenil)-tiazol-4-carboxilato de etilo (1.0 equivalentes) en 2:1 de THF/MeOH (0.17 M), se le agregó LiOH 1.0 M (2.0 equivalentes). Después de reposar durante 16 horas, se agregó HCl 1.0 M (2.0 equivalentes), y el THF/MeOH se removió al vacío. El sólido resultante se filtró, se enjuagó con H_2O y se secó, proporcionando el ácido 2-(2,6-difluoro-fenil)-tiazol-4-carboxílico (88 por ciento) como un sólido de corteza dura. LCMS (*m/z*): 251.1 (MH^+); LC R_t = 2.68 minutos.

Síntesis de ácido 2-ciclohexil-tiazol-4-carboxílico



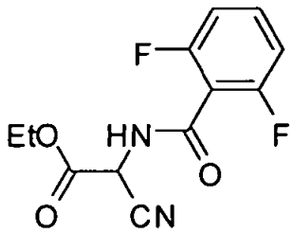
Siguiendo el Método 5, el 2-ciclohexil-tiazol-4-carboxilato de etilo se hidrolizó, proporcionando el ácido 2-ciclohexil-tiazol-4-carboxílico. LCMS (*m/z*): 212.1 (MH^+); LC R_t = 2.90 minutos.

Síntesis de 2-amino-2-ciano-acetato de etilo



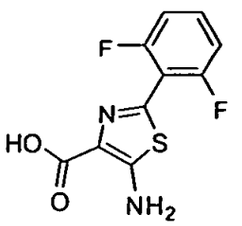
A una solución de 2-ciano-2-(hidroxi-imino)-acetato de etilo (1 equivalente) en 70 mililitros de agua y 56 mililitros de bicarbonato de sodio acuoso saturado, se le agregó en porciones a través de 10 minutos, $Na_2S_2O_4$ (2.8 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La solución se saturó con cloruro de sodio, se extrajo con cloruro de metileno (300 mililitros, 3 veces), y entonces las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, se filtraron, y se concentraron al vacío, para dar el compuesto del título, el cual se utilizó para el siguiente paso sin mayor purificación (55 por ciento). LC/MS (*m/z*): 129.0 (MH^+), R_t: 0.25 minutos.

Síntesis de 2-ciano-2-(2,6-difluoro-benzamido)-acetato de etilo



A una solución del 2-amino-2-ciano-acetato de etilo (1 equivalente) en 6 mililitros de dicloro-metano, se le agregaron piridina (1.5 equivalentes) y cloruro de 2,6-difluoro-benzoilo (1 equivalente) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se diluyó con acetato de etilo, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para dar el compuesto del título (84 por ciento). LC/MS (*m/z*): 269.1 (MH^+), R_t: 0.69 minutos.

Síntesis de ácido 5-amino-2-(2,6-difluoro-fenil)-tiazol-4-carboxílico

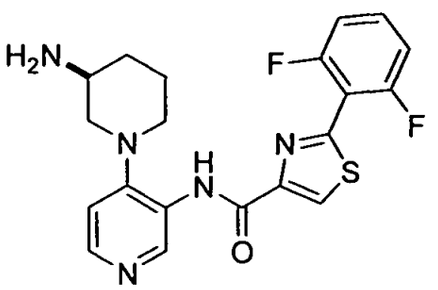


A una solución del 2-ciano-2-(2,6-difluoro-benzamido)-acetato de etilo (1 equivalente) en 10 mililitros de tolueno, se le agregó reactivo de Lawesson. La mezcla se agitó a 95°C durante 2 días. Los solventes se removieron bajo presión reducida. El residuo crudo se purificó mediante cromatografía por evaporación instantánea (EtOAc : hexanos = 1 : 1), para dar el 5-amino-2-(2,6-difluoro-fenil)-tiazol-4-

carboxilato de etilo, el cual se disolvió en 5 mililitros de metanol y 5 mililitros de tetrahidrofurano. Entonces a la mezcla se le agregó hidróxido de sodio 1M (2 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró para remover la mayor parte de los solventes. El residuo se extrajo con acetato de etilo. La capa acuosa se acidificó a un pH = 4-5 mediante HCl 1N. La mezcla resultante se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con salmuera, entonces se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío, para dar el compuesto del título puro (34 por ciento). LC/MS (*m/z*): 257.1 (MH^+), R_t: 0.61 minutos.

Método 6

Síntesis de (S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida



Una solución homogénea de 1 equivalente de cada uno de (S)-1-(3-amino-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, ácido 2-(2,6-difluoro-fenil)-tiazol-4-carboxílico, HOAT, y EDC en NMP, en una concentración de 0.38 M, se dejó reposando durante 48 horas, en cuyo tiempo, la mezcla se purificó directamente mediante HPLC. Después de la liofilización, se obtuvo la sal de ácido trifluoro-acético

del (S)-1-(3-(2-(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-il-carbamato de terbutilo. De una manera alternativa, las fracciones de la HPLC se pudieron agregar al EtOAc y al 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 (S)-1-(3-(2-(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-il-carbamato de terbutilo.

El grupo Boc se removió mediante el tratamiento con ácido trifluoro-acético al 25 por ciento/CH_2Cl_2 durante 2 horas o con un exceso de HCl 4M en dioxano durante 12 horas. Después de la remoción de los volátiles al vacío, el material se purificó mediante HPLC en fase inversa, proporcionando, después de la liofilización, la (S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida como la sal del ácido trifluoro-acético. De una manera alternativa, las fracciones de la HPLC se pudieron agregar al EtOAc y al 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 disolver en MeCN/H_2O, de agregar 1 equivalente de HCl 1N, y de liofilizar, se obtuvo la sal de HCl de la (S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida (43 por ciento). LCMS (*m/z*): 416.1 (MH^+); LC R_t = 1.95 minutos.

Si había hidroxilos protegidos por benzoilo presentes, se pudieron desproteger antes de la remoción del Boc, mediante el tratamiento con hidróxido de sodio 0.2 M (3 equivalentes) en metanol

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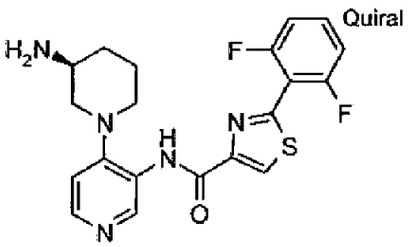
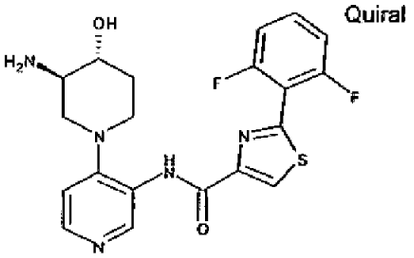
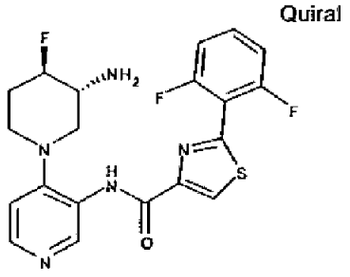
a temperatura ambiente durante 3 horas, después de cuyo tiempo, la solución se diluyó con acetato de etilo, se lavó con salmuera, se secó sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío, para proporcionar el alcohol protegido por Boc.

Si había un carbamato cíclico de N-Boc-1,2-amino-alcohol presente, antes de la desprotección del Boc, se pudo disociar el carbamato cíclico mediante el tratamiento con Cs_2CO_2 (0.5 equivalentes) en metanol en una concentración de 0.1 M durante tres horas. Después de la remoción de los volátiles al vacío, el grupo Boc-amino se desprotegió como se describe anteriormente.

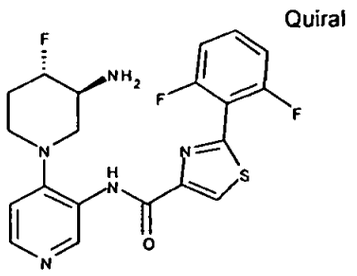
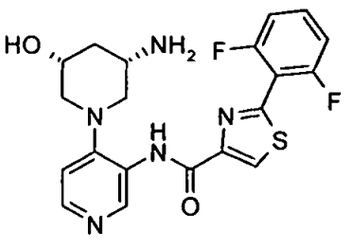
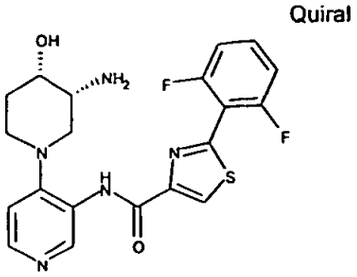
Si había éteres de TBDMS presentes, se desprotegieron antes de la remoción del Boc mediante el tratamiento con HCl 6N, tetrahidrofurano, metanol (1:2:1), a temperatura ambiente durante 2 horas. Después de la remoción de los volátiles al vacío, el grupo Boc-amino se desprotegió como se describe anteriormente.

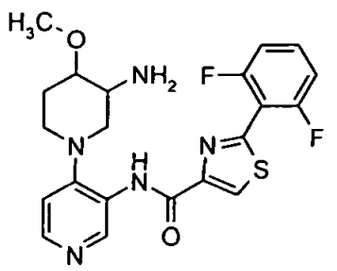
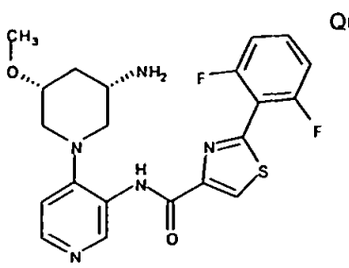
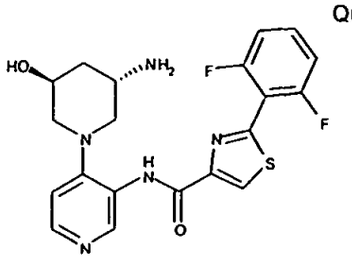
Si había un grupo dietoxi-fosforil-amino presente, la amina se desprotegió mediante calentamiento en una solución 1:1 de dioxano / HCl 2N acuoso a 70°C durante la noche. Después de la remoción de los volátiles al vacío, el material se purificó mediante HPLC en fase inversa.

Los siguientes compuestos se prepararon empleando el Método 6:

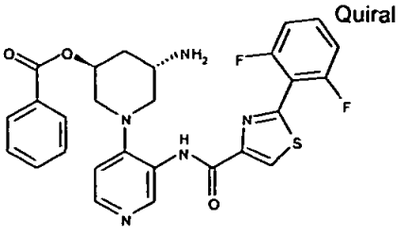
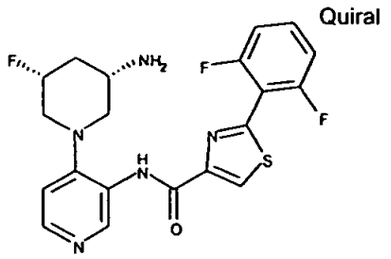
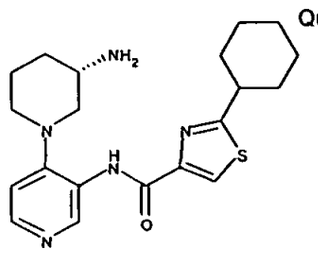
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
1	 Quiral	(S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)- 2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	416.1	1.95
2	 Quiral	N-(4-((3R,4R)-3-amino-4-hidroxi-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	432.1	1.84
3	 Quiral	N-(4-((3R,4R)-3-amino-4-fluoro-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	434.1	2.23

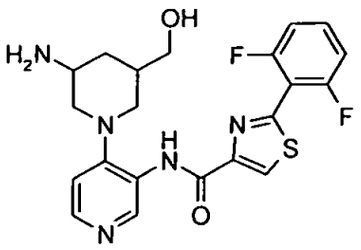
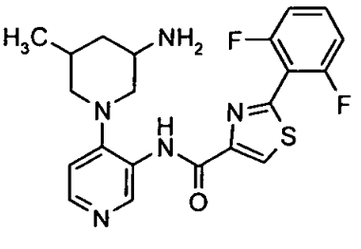
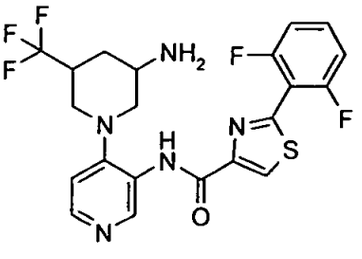
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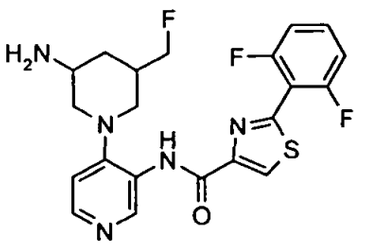
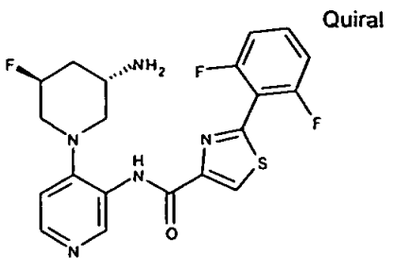
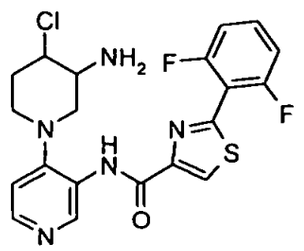
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
4	 Quiral	N-(4-((3S,4S)-3-amino-4-fluoro-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	434.1	2.22
5		N-(4-((3S,5R)-3-amino-5-hidroxi-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	432	1.65
6	 Quiral	N-(4-((3R,4S)-3-amino-4-hidroxi-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	432.1	1.89

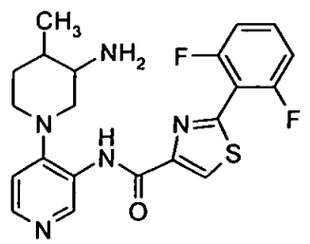
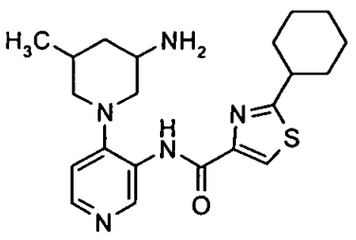
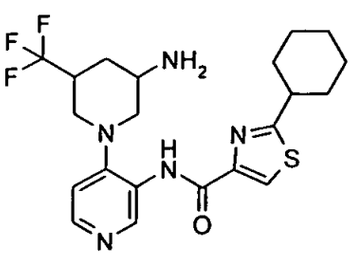
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
7		N-(4-(3-amino-4-metoxi-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	445.9	1.96
8	 Quiral	N-(4-((3S,5R)-3-amino-5-metoxi-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil) tiazol-4-carboxamida	446.1	1.83
9	 Quiral	N-(4-((3S,5S)-3-amino-5-hidroxi-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	432.0	1.75

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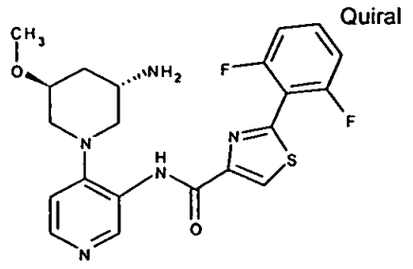
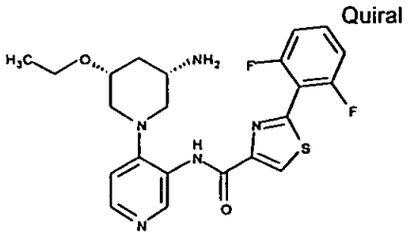
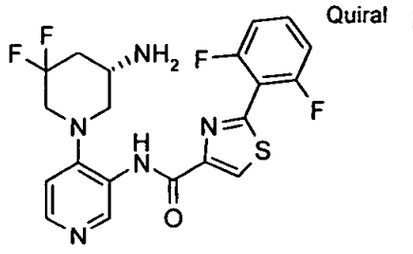
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
10	 Quiral	(3S,5S)- benzoato de 5-amino-1-(3-(2-(2,6-difluoro-fenil) tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-ilo	536.1	2.44
11	 Quiral	N-(4-((3S,5R)-3-amino-5-fluoro-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	433.9	1.80
12	 Quiral	(S)-N-(4-(3-amino-piperidin-1-il) piridin-3-il)-2-ciclohexil-tiazol-4-carboxamida	386.1	2.12

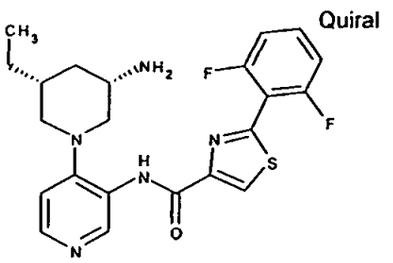
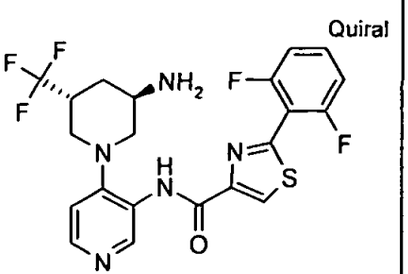
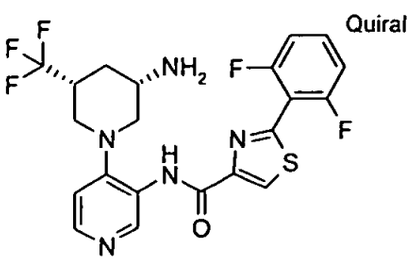
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
13		N-(4-(3-amino-5-(hidroxi-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	446.0	1.78
14		N-(4-(3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	430.0	2.14
15		N-(4-(3-amino-5-(trifluoro-metil) piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	484.1	2.27

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
16		N-(4-(3-amino-5-(fluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil) tiazol-4-carboxamida	448.0	2.05
17	 Quiral	N-(4-((3S,5S)-3-amino-5-fluoro-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	434.0	0.49
18		N-(4-(3-amino-4-cloro-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	449.8	0.55

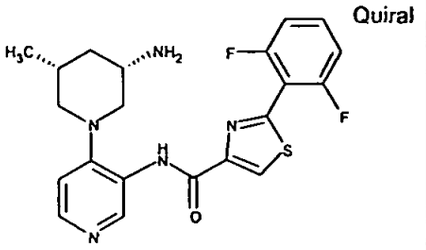
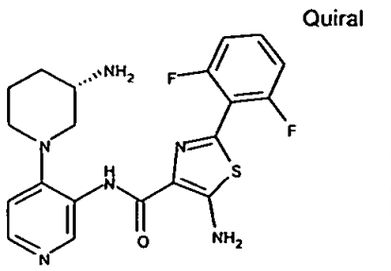
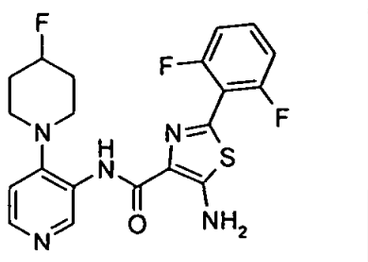
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
19		N-(4-(3-amino-4-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	430.1	0.57
20		N-(4-(3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-ciclohexil-tiazol-4-carboxamida	400.1	0.64
21		N-(4-(3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-ciclohexil-tiazol-4-carboxamida	454.1	0.72

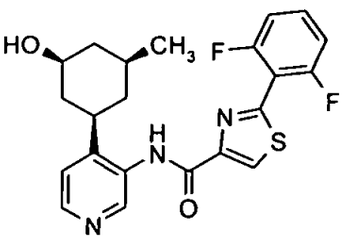
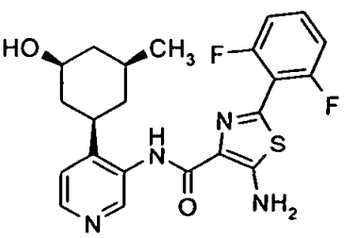
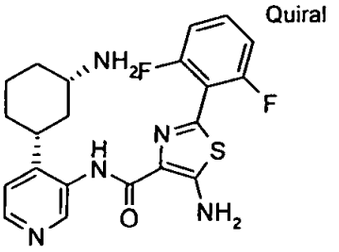
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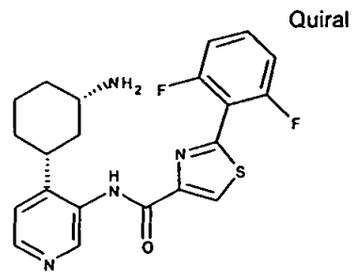
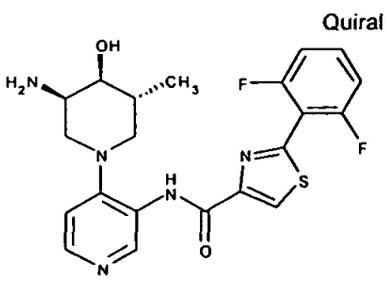
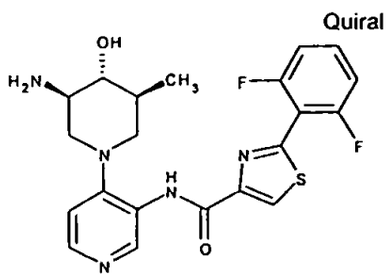
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
22	 Quiral	N-(4-((3S,5S)-3-amino-5-metoxi-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	446.1	0.54
23	 Quiral	N-(4-((3S,5R)-3-amino-5-etoxi-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	460.0	0.54
24	 Quiral	(S)-N-(4-(5-amino-3,3-difluoro-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	452.0	0.56

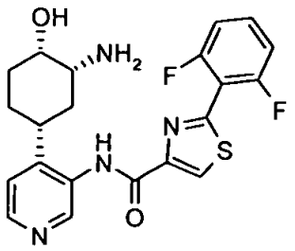
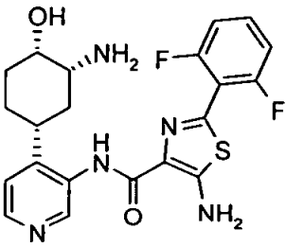
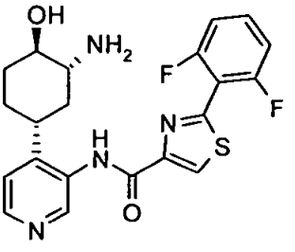
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
25		N-(4-((3S,5R)-3-amino-5-etil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	444.1	0.57
26		N-(4-((3R,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	484.1	0.57
27		N-(4-((3S,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	484.0	0.68

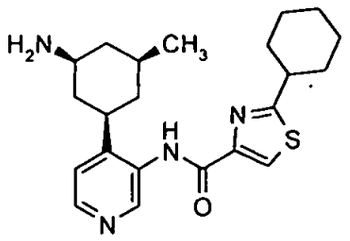
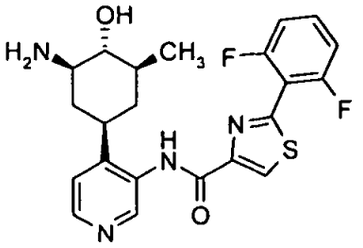
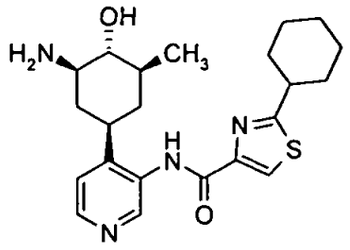
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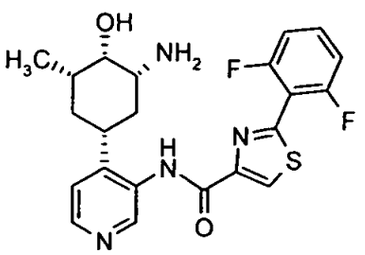
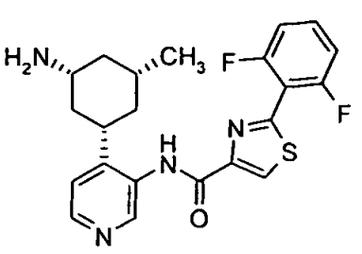
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
28	 Quiral	N-(4-((3S,5R)-3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	430.2	0.60
29	 Quiral	(S)-5-amino-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	431.0	0.51
30		5-amino-2-(2,6-difluoro-fenil)-N-(4-(4-fluoro-piperidin-1-il)-piridin-3-il)-tiazol-4-carboxamida	434.0	0.75

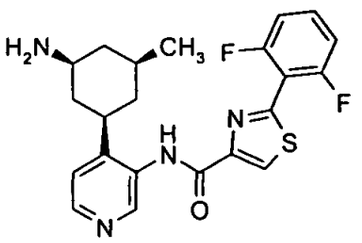
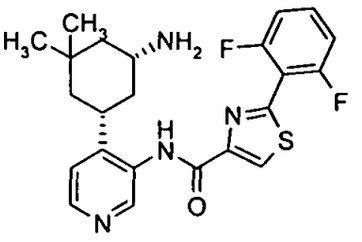
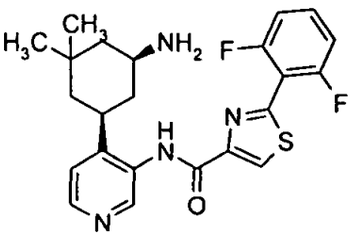
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
31		2-(2,6-difluoro-fenil)-N-(4-((1R,3S,5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida	430.1	0.7
32		5-amino-2-(2,6-difluoro-fenil)-N-(4-((1R,3S,5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida	445.1	0.7
33		5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	430.0	0.54

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
34	 Quiral	N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	415.0	0.54
35	 Quiral	N-(4-((3R,4S,5R)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	446.2	0.51
36	 Quiral	N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	446.0	0.55

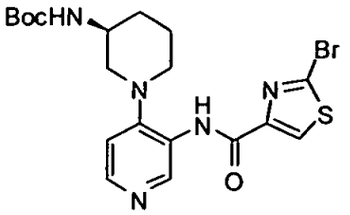
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
37		N-(4-((1R,3R,4S)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	431.0	0.50
38		5-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	446.1	0.51
39		N-(4-((1R,3R,4R)-3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	431.0	0.54

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
40		N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-ciclohexil-tiazol-4-carboxamida	399.3	0.63
41		N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida (y enantiómero)	445.1	0.52
42		N-(4-((1R,3R,4R,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-2-	415.1	0.60

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
		ciclohexil-tiazol-4-carboxamida		
43		N-(4-((1R,3R,4S,5S)-3-amino-4-hidroxi-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida (y enantiómero)	445.2	0.54
44	Quiral 	N-(4-((1S,3R,5R)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	429.2	0.68

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
45	Quiral 	N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	429.2	0.68
46	Quiral 	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	443.2	0.60
47	Quiral 	N-(4-((1R,5R)-5-amino-3,3-dimetil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida	443.2	0.60

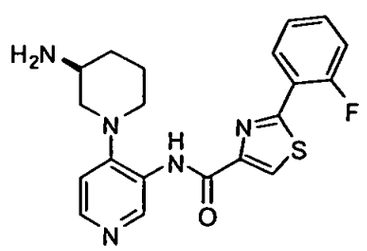
Síntesis de (S)-1-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-il-carbamato de terbutilo



Una solución que contiene 1 equivalente de cada uno de (S)-1-(3-amino-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, ácido 2-bromo-tiazol-4-carboxílico, HOAT, y EDC en N,N-dimetil-formamida, en una concentración de 0.5 M, se agitó durante 60 horas. La solución se diluyó con EtOAc, y se lavó con H_2O (4 veces), NaCl saturado, se secó sobre $MgSO_4$, se filtró, y los volátiles se removieron al vacío, proporcionando el (S)-1-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-il-carbamato de terbutilo, LCMS (*m/z*): 416.1 (MH^+); LC R_t = 1.95 minutos.

Método 7

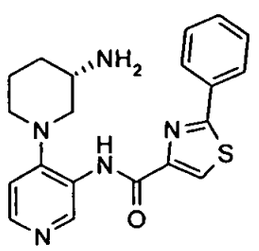
Síntesis de (S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2-fluoro-fenil)-tiazol-4-carboxamida

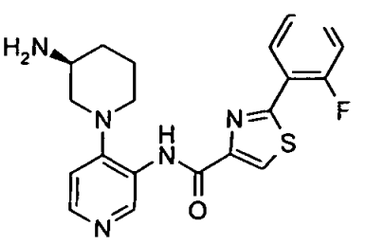
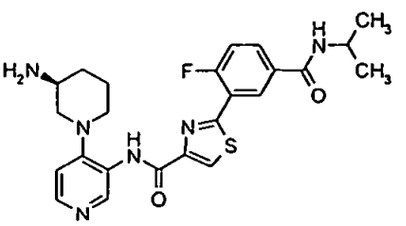
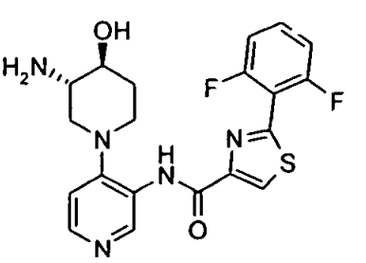


Una solución de (S)-1-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-piperidin-3-il-carbamato de terbutilo (1.0 equivalentes), ácido 2-fluoro-fenil-borónico (3.0 equivalentes), $Pd(dppf)Cl_2$-CH_2Cl_2

(0.15 equivalentes) en 3:1 DME/$Na_2CO_3$2M (concentración = 0.1 M) se calentó a 120°C con irradiación con microondas durante 1,200 segundos. Después de enfriarse, la capa orgánica se separó, se concentró, y el producto de N-Boc de Suzuki se purificó directamente mediante HPLC en fase inversa. La fracción del producto se liofilizó, y el sólido resultante se trató con ácido trifluoro-acético al 25 por ciento/dicloro-metano (en una concentración resultante de 0.05 M). Después de asentarse durante 2 horas, los volátiles se removieron al vacío, y el residuo se purificó mediante HPLC en fase inversa. Después de la liofilización, se obtuvo la (S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2-fluoro-fenil)-tiazol-4-carboxamida (35 por ciento) como la sal del ácido trifluoro-acético. LCMS (m/z): 398.1 (MH+); LC Rt = 2.06 minutos.

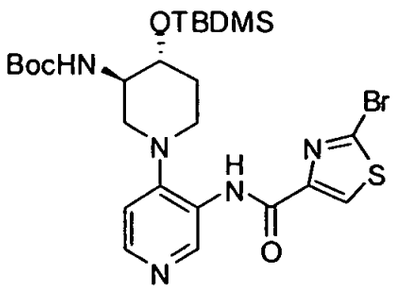
Los siguientes compuestos se prepararon empleando el Método 7:

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
48	Quiral 	(S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-fenil-tiazol-4-carboxamida	380.1	1.94

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
49	Quiral 	(S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2-fluoro-fenil) tiazol-4-carboxamida	398.1	2.06
50	Quiral 	(S)-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2-fluoro-5-(isopropil-carbamoil)-fenil)-tiazol-4-carboxamida	483.2	2.04
51	Quiral 	N-(4-((3S,4S)-3-amino-4-hidroxi-piperidin-1-il) piridin-3-il)-2-(2,6-difluoro fenil)-tiazol-4-	432.1	1.85

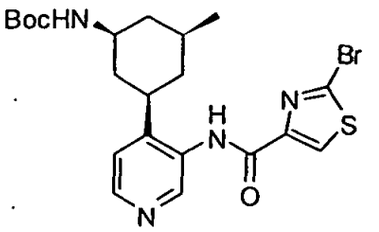
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
		carboxamida		

Síntesis de (3R,4R)-1-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo



Una solución que contiene 1 equivalente de cada uno de (3R,4R)-1-(3-amino-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, ácido 2-bromo-tiazol-4-carboxílico, HOAT, y EDC en N,N-dimetil-formamida, en una concentración de 0.5 M, se agitó durante 60 horas. La solución se diluyó con EtOAc, y se lavó con H_2O (4 veces), NaCl saturado, se secó sobre $MgSO_4$, se filtró y los volátiles se removieron al vacío, proporcionando el (3R,4R)-1-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-4-(terbutil-dimetil-sililoxi)-piperidin-3-il-carbamato de terbutilo, LCMS (*m/z*): 612.2/614.2 (MH^+); LC R_t = 4.26 minutos.

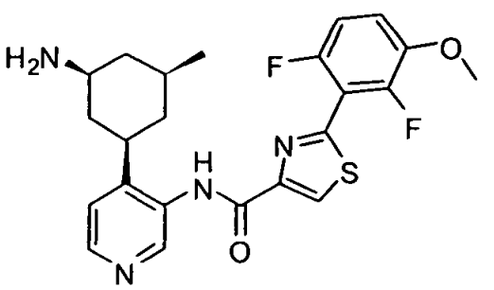
Síntesis de (1S,3R,5S)-3-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo



Una solución que contiene 1 equivalente de cada uno de (1S,3R,5S)-3-(3-amino-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo, ácido 2-bromo-tiazol-4-carboxílico, HOAT, y EDC en N,N-dimetil-formamida, en una concentración de 0.3 M, se agitó durante 17 horas. La solución se diluyó con EtOAc, y se lavó con H_2O (4 veces), NaCl saturado, se secó sobre $MgSO_4$, se filtró, y los volátiles se removieron al vacío, proporcionando el (1S,3R,5S)-3-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo, LCMS (*m/z*): 495.1/497.1 (MH^+); LC R_t = 3.17 minutos.

Método 8

Síntesis de N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida



Una solución del (1S,3R,5S)-3-(3-(2-bromo-tiazol-4-carboxamido)-piridin-4-il)-5-metil-ciclohexil-carbamato de terbutilo (1.0 equivalentes), ácido 2,6-difluoro-3-metoxi-fenil-borónico (4.0 equivalentes), DIEA (4.0 equivalentes), y $Pd(PPh_3)_4$ (0.2

equivalentes) en 1:1 de tolueno/etanol en una concentración de 0.03 M, se calentó en microondas a 120°C durante 20 minutos. La solución se volvió a someter a calentamiento en microondas a 130°C durante 30 minutos, 2 veces. Los solventes se removieron al vacío, y el residuo se purificó mediante HPLC. Las fracciones del producto se liofilizaron directamente, para proporcionar el producto de amida protegido como la sal del ácido trifluoro-acético. El grupo Boc se desprotegió mediante el tratamiento con ácido trifluoro-acético al 25 por ciento/CH_2Cl_2 durante dos horas. Después de la remoción de los volátiles al vacío, el producto se purificó mediante HPLC, para proporcionar la N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida.

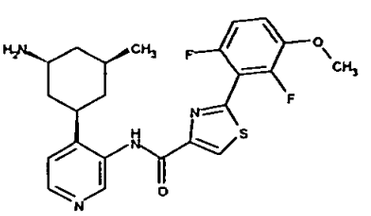
LCMS (*m/z*): 459.2 (MH^+); LC R_t = 2.32 minutos.

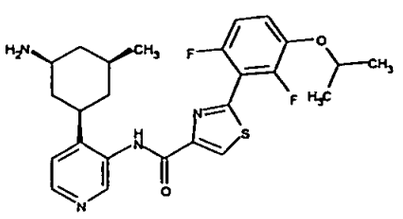
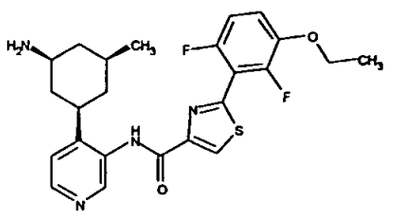
Cuando se aplicó el método anterior para Suzuki, a veces fue necesario volver a someter a calentamiento en microondas, y adicionalmente agregar más de ácido borónico (4.0 equivalentes), DIEA (4.0 equivalentes), y $Pd(PPh_3)_4$ (0.2 equivalentes) con cada re-sometimiento.

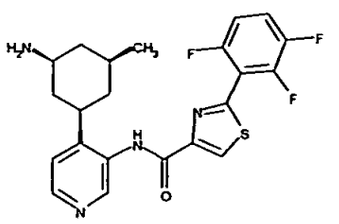
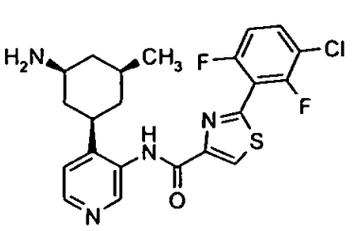
De una manera alternativa, las reacciones de Suzuki con ácidos borónicos 2,6-difluoro-sustituidos y 2-bromo-4-carboxamido-tiazoles, se pueden llevar a cabo mediante calentamiento del bromuro (1.0 equivalentes), ácido borónico (5 equivalentes), KF (5.5 equivalentes), tri-terbutil-fosfina (0.4 equivalentes), y $Pd_2(dba)_3$ (0.2 equivalentes) en 10:1 de THF/H_2O en una concentración de 0.03 M en microondas a 100°C durante 30 minutos. Con este método, a

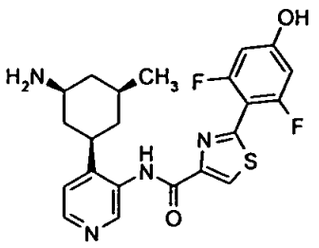
veces es necesario volver a someter a calentamiento en microondas a 100°C, y adicionalmente agregar más de ácido borónico (5.0 equivalentes), KF (5.5 equivalentes), tri-terbutil-fosfina (0.4 equivalentes), y $Pd_2(dba)_3$ (0.2 equivalentes) con cada re-sometimiento.

Los siguientes compuestos se prepararon empleando el Método 8:

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
52	Quiral 	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxilico	459.2	0.58

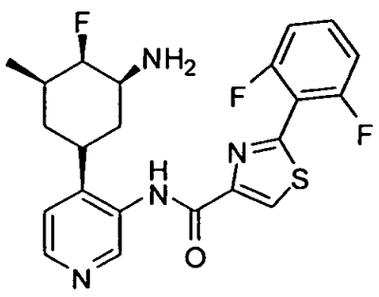
Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
53	Quiral 	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-[2-fluoro-1-(1-fluoro-vinil)-3-isopropoxi-propenil]-tiazol-4-carboxílico	487.3	0.67
54	Quiral 	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(3-etoxi-2,6-difluoro-fenil)-tiazol-4-	473.3	0.63

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
		carboxílico		
55	Quiral 	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,3,6-trifluoro-fenil)-tiazol-4-carboxílico	447.2	0.59
56	Quiral 	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(3-cloro-2,6-difluoro-fenil)-tiazol-4-carboxílico	463.1	0.62

Ej. No.	Estructura	Nombre del Compuesto	LC/MS (M+H en UPCL)	LC/MS (Rf min en UPLC)
57	 Quiral	[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico	445.2	0.54

Ejemplo 58

Síntesis de N-(4-((+/-)-3-amino-4-fluoro-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida



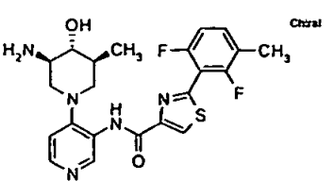
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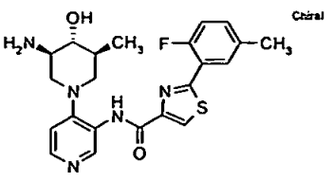
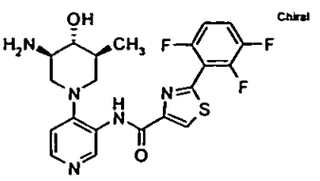
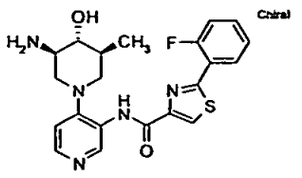
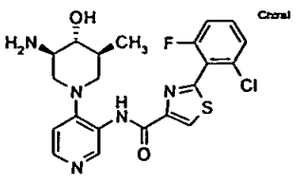
(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-6-metil-ciclohexil-acetato en metanol (0.03 M), se le agregó carbonato de potasio (3.0 equivalentes) y la reacción se agitó a temperatura ambiente durante 3 horas. Al completarse, la reacción se dividió entre agua y acetato de etilo. La fase acuosa se extrajo adicionalmente 3 veces más con acetato de etilo. Los orgánicos se combinaron, se secaron con salmuera y sulfato de sodio, se filtraron, y se concentraron. Se obtuvo el (+/-)-5-(3-(2-(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-2-hidroxi-3-metil-ciclohexil-carbamato de terbutilo aislado como un sólido grisáceo en un 87 por ciento de rendimiento. LC/MS = 545.2 (M+H), Rt = 0.75 minutos.

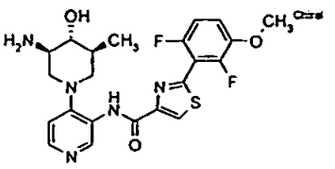
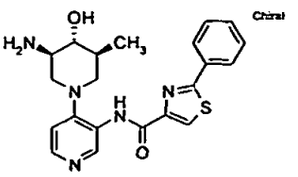
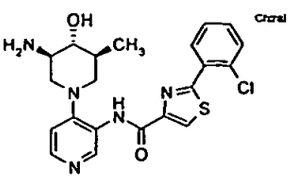
A una solución del (+/-)-5-(3-(2-(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-2-hidroxi-3-metil-ciclohexil-carbamato de terbutilo (1.0 equivalentes) en dicloro-metano (0.07M) a 0°C, se le agregó DAST (1.0 equivalentes) bajo una atmósfera de nitrógeno. La reacción se agitó durante 1 hora, después de cuyo tiempo, se agregaron 2 equivalentes más de DAST. Después de 30 minutos, se completó el consumo del material de partida. La reacción se apagó mediante la adición de agua, la fase orgánica se secó con sulfato de sodio, 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 (+/-)-5-(3-(2-(2,6-difluoro-fenil)-tiazol-4-carboxamido)-piridin-4-il)-2-fluoro-3-metil-ciclohexil-carbamato de terbutilo como un aceite transparente en un 60 por ciento de rendimiento. LC/MS = 547.3 (M+H), Rt = 0.92 minutos. El

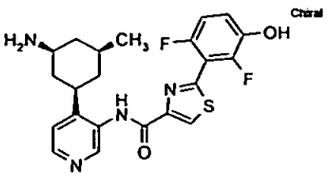
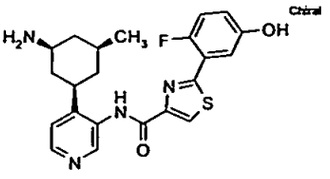
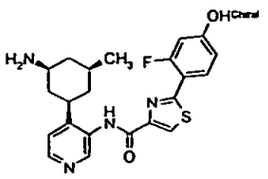
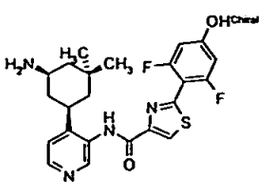
grupo Boc se removió mediante el tratamiento con ácido trifluoro-acético al 25 por ciento en dicloro-metano durante 2 horas. Después de la concentración al vacío, el producto crudo se purificó por medio de HPLC de semi-preparación. Las fracciones puras se liofilizaron para proporcionar la N-(4-((+/-)-3-amino-4-fluoro-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida como el producto deseado, como la sal del ácido trifluoro-acético en un 74 por ciento de rendimiento. LC/MS = 447.0 (M+H), Rt = 0.56 minutos.

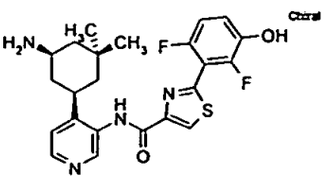
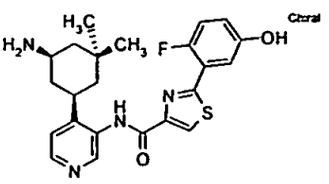
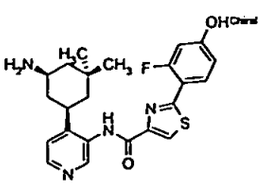
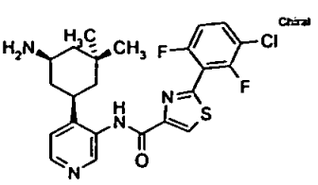
Los siguientes compuestos se preparan utilizando las técnicas y los procedimientos descritos en la presente.

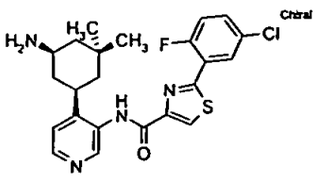
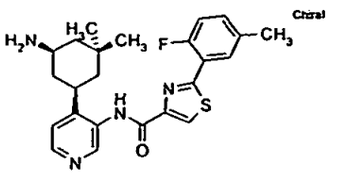
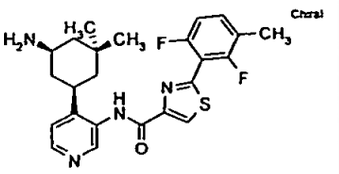
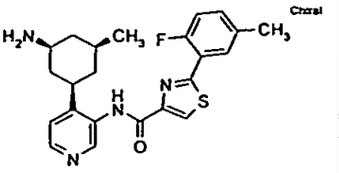
Ejemplo	Estructura	Nombre
59		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-3-metil-fenil)-tiazol-4-carboxílico

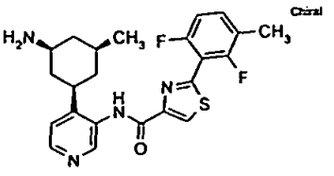
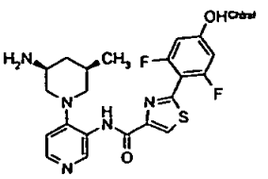
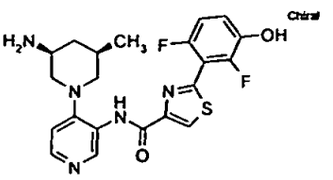
Ejemplo	Estructura	Nombre
60		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-5-metil-fenil)-tiazol-4-carboxílico
61		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,3,6-trifluoro-fenil)-tiazol-4-carboxílico
62		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-fenil)-tiazol-4-carboxílico
63		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-cloro-6-fluoro-fenil)-tiazol-4-carboxílico

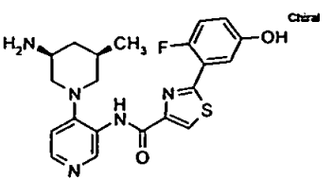
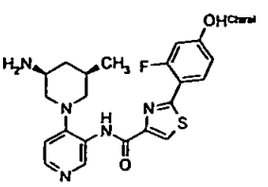
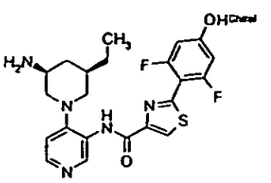
Ejemplo	Estructura	Nombre
64		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxílico
65		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-fenil-tiazol-4-carboxílico
66		(3-amino-4-hidroxi-5-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-cloro-fenil)-tiazol-4-carboxílico

Ejemplo	Estructura	Nombre
67		[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico
68		[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico
69		[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
70		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico

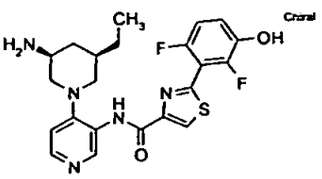
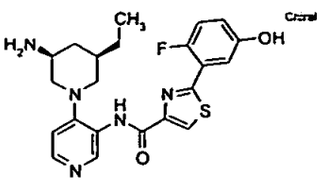
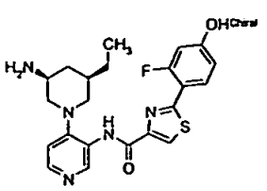
Ejemplo	Estructura	Nombre
71		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico
72		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico
73		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
74		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(3-cloro-2,6-difluoro-fenil)-tiazol-4-carboxílico

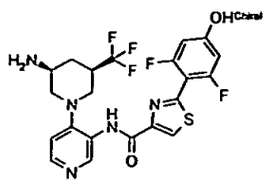
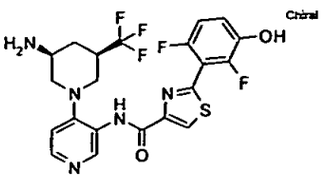
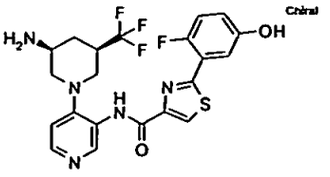
Ejemplo	Estructura	Nombre
75		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(5-cloro-2-fluoro-fenil)-tiazol-4-carboxílico
76		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-metil-fenil)-tiazol-4-carboxílico
77		[4-(5-amino-3,3-dimetil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-metil-fenil)-tiazol-4-carboxílico
78		[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-metil-fenil)-tiazol-4-carboxílico

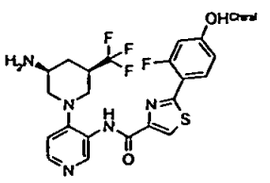
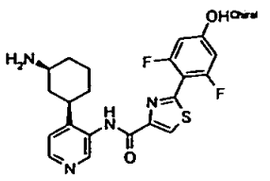
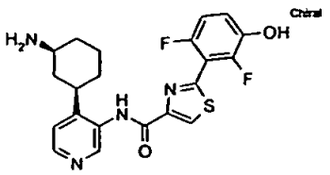
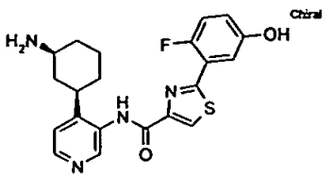
Ejemplo	Estructura	Nombre
79		[4-(3-amino-5-metil-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-metil-fenil)-tiazol-4-carboxílico
80		(5-amino-3-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
81		(5-amino-3-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico

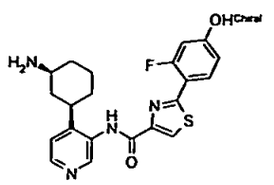
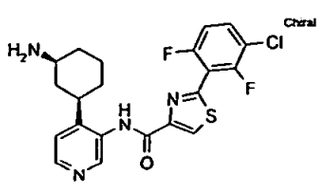
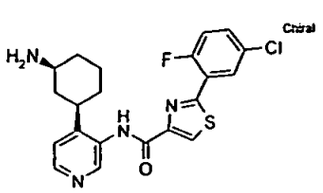
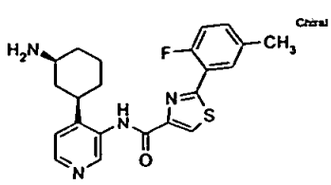
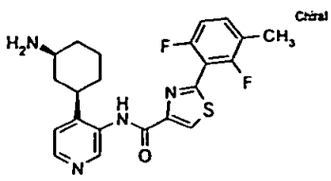
Ejemplo	Estructura	Nombre
82		(5-amino-3-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico
83		(5-amino-3-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
84		(5-amino-3-etil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico

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Ejemplo	Estructura	Nombre
85		(5-amino-3-etil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico
86		(5-amino-3-etil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico
87		(5-amino-3-etil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico

Ejemplo	Estructura	Nombre
88		(5-amino-3-trifluoro-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
89		(5-amino-3-trifluoro-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico
90		(5-amino-3-trifluoro-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico

Ejemplo	Estructura	Nombre
91		(5-amino-3-trifluoro-metil-3,4,5,6-tetrahidro-2H-[1,4']-bipiridinil-3'-il)-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
92		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
93		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-hidroxi-fenil)-tiazol-4-carboxílico
94		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-hidroxi-fenil)-tiazol-4-carboxílico

Ejemplo	Estructura	Nombre
95		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-4-hidroxi-fenil)-tiazol-4-carboxílico
96		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(3-cloro-2,6-difluoro-fenil)-tiazol-4-carboxílico
97		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(5-cloro-2-fluoro-fenil)-tiazol-4-carboxílico
98		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2-fluoro-5-metil-fenil)-tiazol-4-carboxílico
99		[4-(3-amino-ciclohexil)-piridin-3-il]-amida del ácido 2-(2,6-difluoro-3-metil-fenil)-tiazol-4-carboxílico

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 amortiguador 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 amortiguador 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 la tabla 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*.

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 amortiguador 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 amortiguador 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 la tabla que se encuentra más adelante.

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 amortiguador 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 80 µM en amortiguador 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 la tabla que se encuentra más adelante.

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.

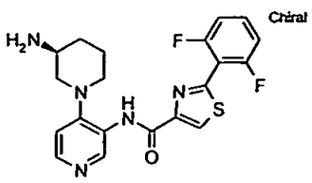
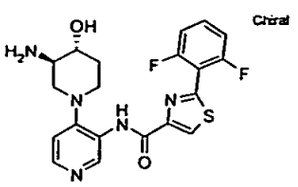
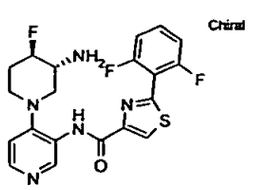
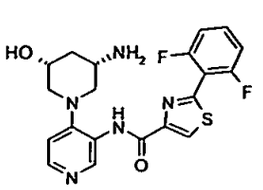
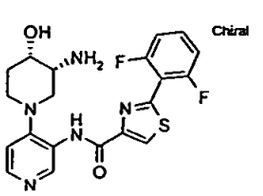
Después de 3 días, las placas se equilibraron a temperatura ambiente, y se agregó un volumen igual de Reactivo Cell Titer-Glow (Promega) a las cavidades de cultivo. Las placas se agitaron

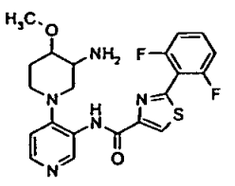
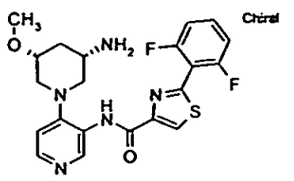
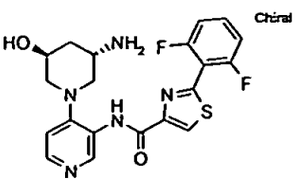
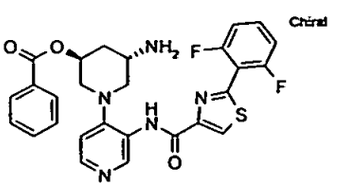
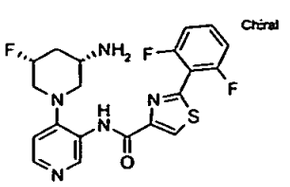
brevemente, y la señal luminiscente se midió con el luminómetro. Se calculó el porcentaje de inhibición de la señal que se ve en las células tratadas con sulfóxido de dimetilo solamente contra las células tratadas con el compuesto de control, y se utilizó para determinar los valores EC_{50} (es decir, 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 la tabla que se encuentra más adelante.

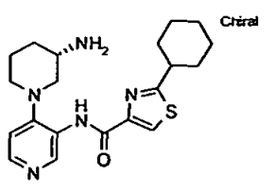
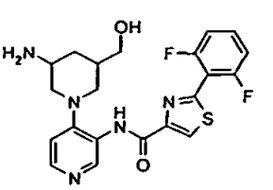
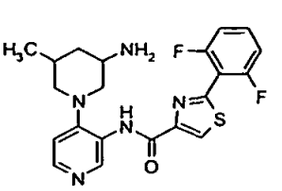
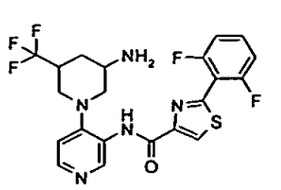
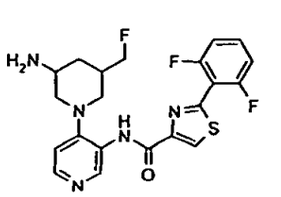
Actividad IC_{50} y EC_{50} de los Compuestos de la Invención

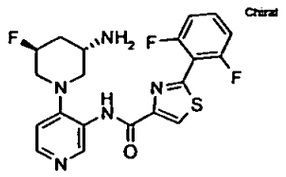
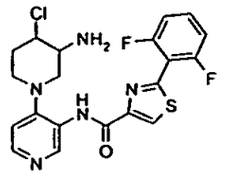
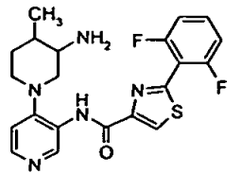
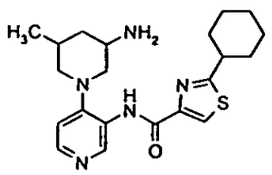
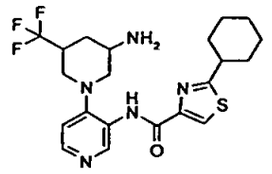
Empleando los procedimientos para el ensayo de agotamiento de ATP de Pim 1 (PIM-1), para el ensayo de agotamiento de ATP de Pim 2 (PIM-2), y para el ensayo de agotamiento de ATP de Pim 3 (PIM-3), descritos anteriormente, se determinó la concentración IC_{50} de los compuestos de los ejemplos anteriores, como se muestra en la siguiente tabla.

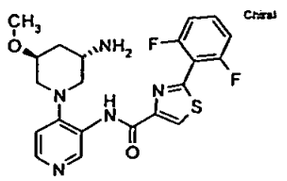
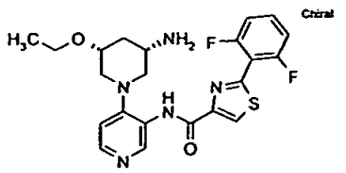
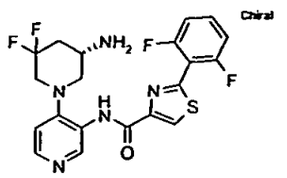
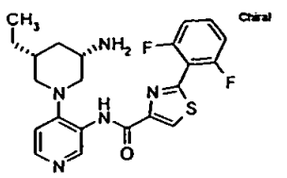
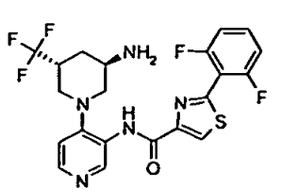
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)

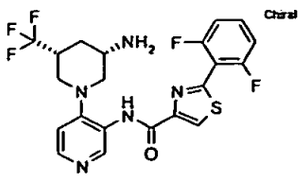
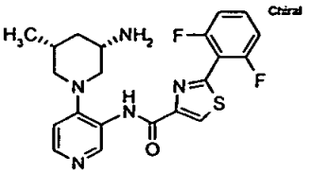
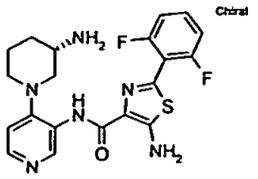
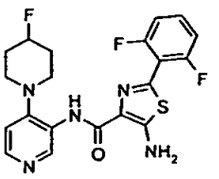
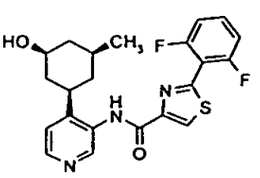
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
1		0.001	0.008	0.002
2		0.002	0.011	0.004
3		0.002	0.023	0.005
5		0.015	0.077	0.013
6		0.001	0.003	0.001

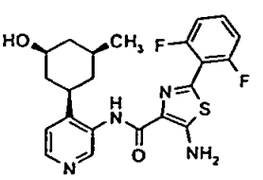
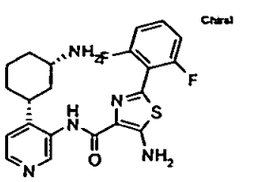
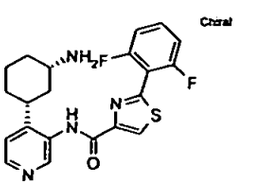
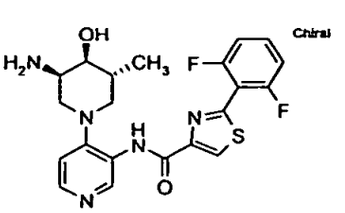
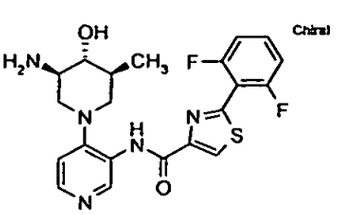
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
7		0.005	0.243	0.018
8		0.021	0.046	0.035
9		0.069	1.502	0.091
10		2.220	0.479	0.322
11		0.004	0.055	0.008

Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
12		0.057	0.208	0.045
13		0.014	0.058	0.024
14		0.002	0.004	0.005
15		0.001	0.003	0.004
16		0.001	0.003	0.004

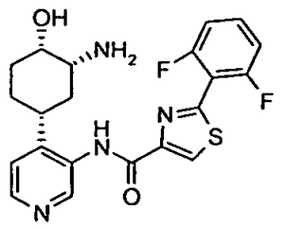
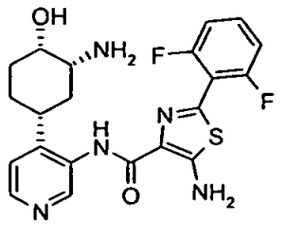
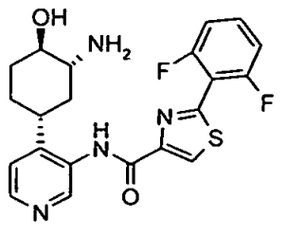
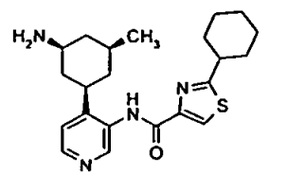
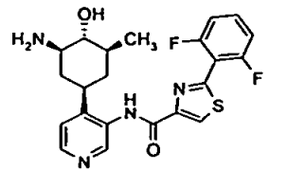
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
17		0.004	0.070	0.008
18		0.005	0.054	0.012
19		0.001	0.008	0.005
20		0.012	0.018	0.016
21		0.011	0.021	0.020

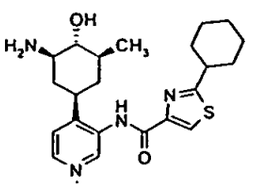
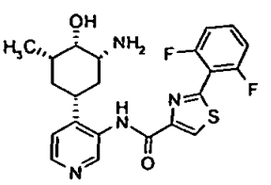
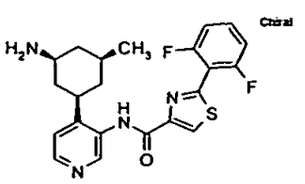
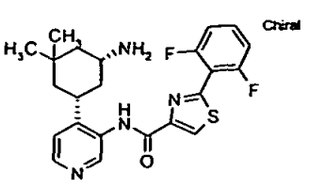
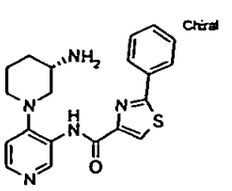
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
22		0.129	0.378	0.060
23		0.056	0.085	0.086
24		0.002	0.038	0.004
25		0.001	0.003	0.003
26		0.006	0.072	0.024

Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
27		0.001	0.003	0.003
28		0.001	0.002	0.002
29		0.001	0.002	0.002
30		0.001	0.055	0.003
31		0.002	0.090	0.008

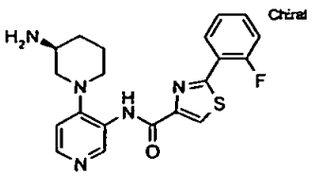
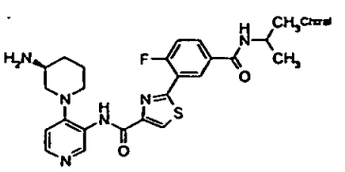
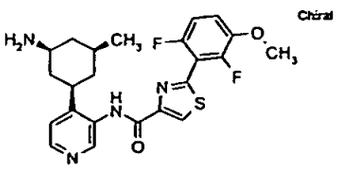
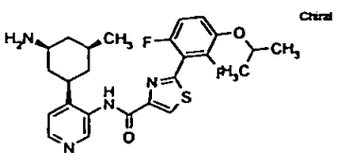
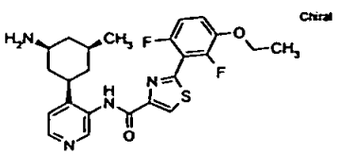
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
32		0.001	0.005	0.004
33		0.001	0.003	0.003
34		0.002	0.029	0.004
35		0.009	0.125	0.009
36		0.001	0.003	0.003

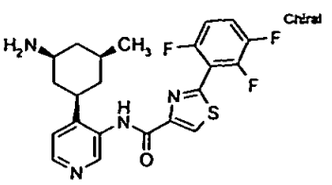
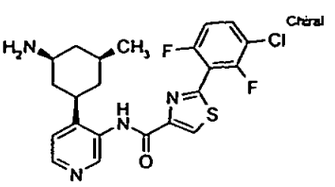
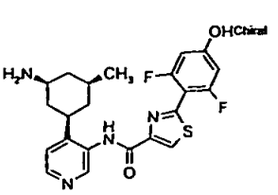
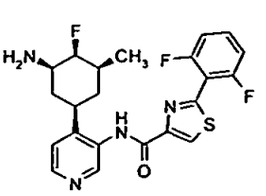
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Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
37		0.006	0.098	0.011
38		0.001	0.004	0.003
39		0.011	0.095	0.012
40		0.041	0.097	0.109
41		0.004	0.027	0.008

Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
42		0.146	0.250	0.215
43		0.005	0.046	0.015
45		0.001	0.007	0.003
46		0.001	0.016	0.003
48		0.0020	0.0177	0.0023

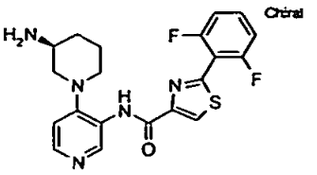
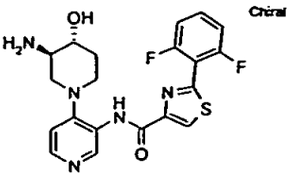
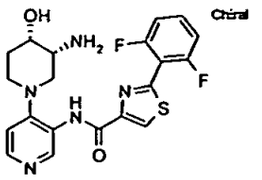
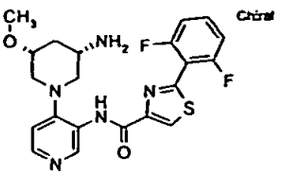
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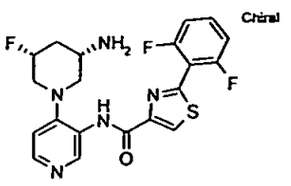
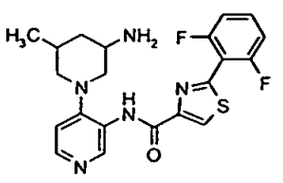
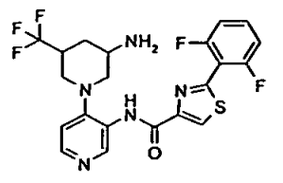
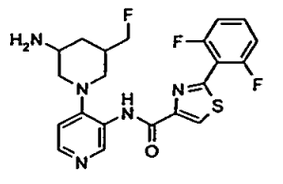
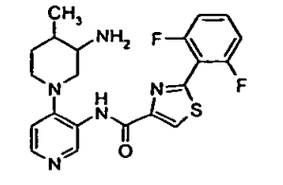
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
49		0.0019	0.0099	0.0042
50		0.0032	0.0838	0.0083
52		0.001	0.004	0.002
53		0.001	0.020	0.003
54		0.001	0.009	0.003

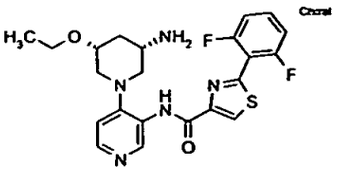
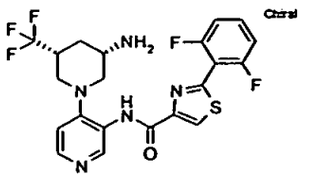
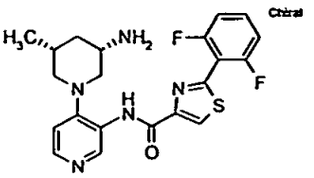
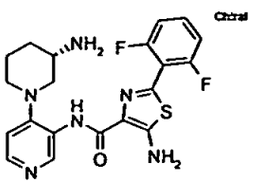
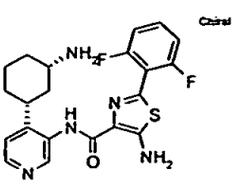
Ej. No.	Estructura	Pim1 IC_{50} (μM	Pim2 IC_{50} (μM)	Pim3 IC_{50} (μM)
55		0.003	0.015	0.005
56		0.001	0.012	0.003
57		0.001	0.004	0.002
58		0.004	0.047	0.018

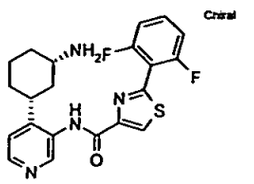
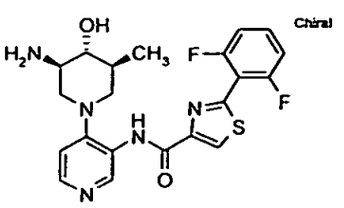
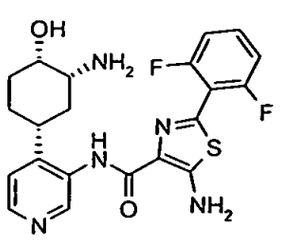
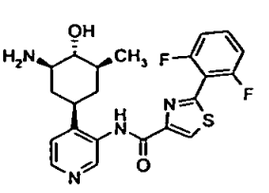
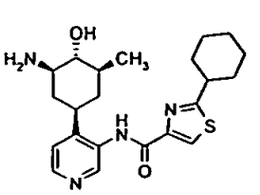
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Empleando los procedimientos para el Ensayo de Proliferación Celular descrito anteriormente, se determinó la concentración EC_{50} de los compuestos de los ejemplos anteriores en células KMS11, como se muestra en la siguiente Tabla.

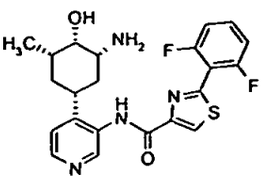
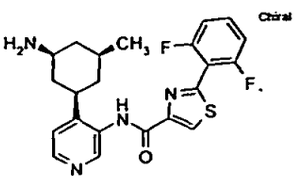
Ej. No.	Estructura	KMS11 EC_{50} (μM)
1		1.17
2		1.57
6		0.41
8		4.70

Ej. No.	Estructura	KMS11 EC_{50} (μM)
11		6.10
14		0.83
15		0.31
16		2.38
19		0.93

Ej. No.	Estructura	KMS11 EC_{50} (μM)
23		6.54
27		0.46
28		0.40
29		0.04
33		0.43

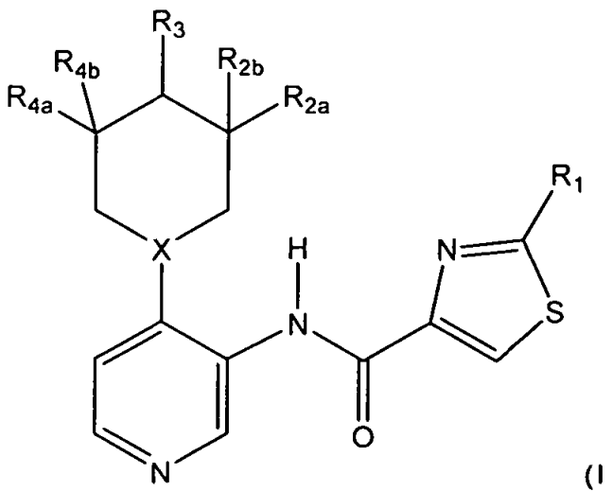
Ej. No.	Estructura	KMS11 EC_{50} (μM)
34		5.02
36		0.56
38		1.89
41		>10
42		

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Ej. No.	Estructura	KMS11 EC_{50} (μM)
43		
45		0.92

REIVINDICACIONES

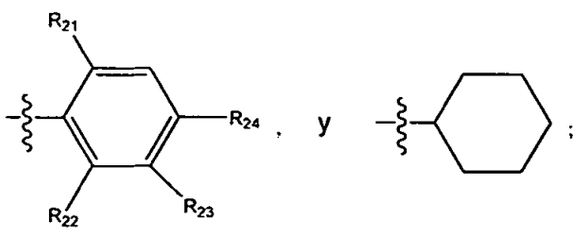
1. Un compuesto de la fórmula I, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



(I)

en donde:

R_1 se selecciona a partir de:



X representa CH o N;

R_{2a} se selecciona a partir de amino, metilo, CH_2F, CF_3, C_{2H5}, y H;

R_{2b} se selecciona a partir de H, y metilo;

R_3 se selecciona a partir de H, OH, OCH_3, CH_3, F, y Cl;

R_{4a} se selecciona a partir de amino, metilo, OH, OCH_3, OC_2H_5, F, CF_3, H, y etilo;

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R_{4b} se selecciona a partir de metilo, H, y F;

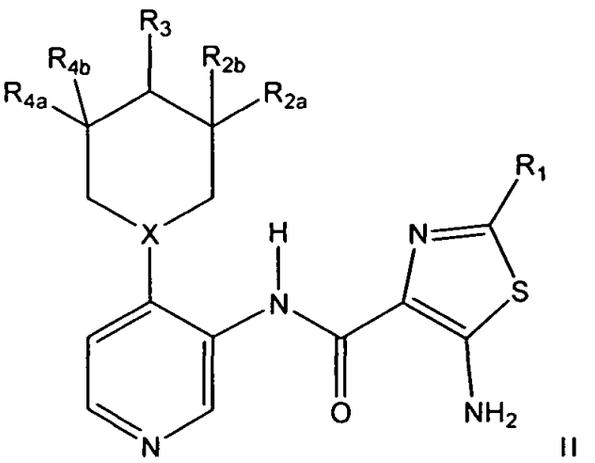
R_{21} representa H o F;

R_{22} representa H, Cl, o F;

R_{23} representa F, OC_2H_5, OCH_3, Cl, H, metilo, OH, u $OCH(CH_3)_2$; y

R_{24} representa H u OH.

2. Un compuesto de la fórmula II, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo:



II

en donde:

R_1 se selecciona a partir de -NH-CO-alquilo, cicloalquilo sustituido o insustituido, hetero-cicloalquilo sustituido o insustituido, arilo sustituido o insustituido, y hetero-arilo sustituido o insustituido;

X representa CH o N;

R_{2a} se selecciona a partir de -H, -OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno, amino y benzoato;

R_{2b} se selecciona a partir de –H y alquilo;

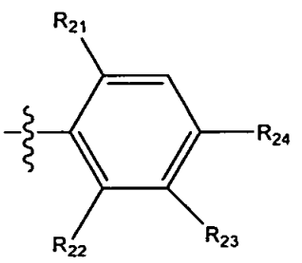
R_3 se selecciona a partir de H, OH, alquilo, alcoxilo y halógeno;

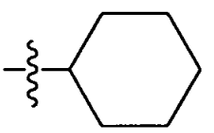
R_{4a} se selecciona a partir de –OH, alquilo, alcoxilo, halo-alquilo, amino-alquilo, hidroxi-alquilo, halógeno, y amino; y

R_{4b} se selecciona a partir de H, alquilo y halógeno.

3. Un compuesto de la reivindicación 2 en donde R_1 se selecciona a partir de fenilo sustituido o insustituido, ciclohexilo sustituido o insustituido, y piperidinilo sustituido o insustituido.

4. Un compuesto de la reivindicación 3 en donde R_1 se selecciona a partir de:



, y  ;

en donde:

R_{21} es H o halógeno;

R_{22} es H o halógeno;

R_{23} se selecciona a partir de H, halógeno, alquilo y alcoxilo; y

R_{24} es H o OH;

5. Un compuesto de la reivindicación 4, en donde R_{21} y R_{22} se seleccionan independientemente a partir de H o F.

6. Un compuesto de la reivindicación 4, en donde R_{23} se

selecciona a partir de H, Cl, F, $-OC_2H_5$, $-OCH_3$, y $-OCH(CH_3)_2$.

7. Un compuesto de la reivindicación 2, en donde R_2 se selecciona a partir de H, metilo, etilo, metoxilo, etoxilo, fluoro-metilo, trifluoro-metilo, amino-metilo e hidroxi-metilo.

8. Un compuesto de la reivindicación 2, en donde R_3 se selecciona a partir de H, -OH, metilo, metoxilo, F y Cl.

9. Un compuesto de la reivindicación 2, en donde R_{4a} se selecciona a partir de -OH, metilo, etilo, trifluoro-metilo, metoxilo, etoxilo, amino, F y Cl.

10. Un compuesto de la reivindicación 2, en donde R_{4b} se selecciona a partir de metilo y F.

11. Un compuesto de la reivindicación 1 o de la reivindicación 2, seleccionado a partir del grupo que consiste en (S)-5-amino-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-etil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-

4-carboxamida, N-(4-(3-amino-5-(fluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida, 5-amino-2-(2,6-difluoro-fenil)-N-(4-((1R,3S,5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-(3-amino-4-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(3-etoxi-2,6-difluoro-fenil)-tiazol-4-carboxamida, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de las mismas.

12. Un compuesto de la reivindicación 1 ó 2, seleccionado a partir del grupo que consiste en (S)-5-amino-N-(4-(3-amino-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3R,4R,5S)-3-amino-4-hidroxi-5-metil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-((1R,3S)-3-amino-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-(trifluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((3S,5R)-3-amino-5-etil-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-4-hidroxi-fenil)-tiazol-4-carboxamida, 5-amino-N-(4-(3-amino-4-hidroxi-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-(3-

amino-5-(fluoro-metil)-piperidin-1-il)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-3-metoxi-fenil)-tiazol-4-carboxamida, 5-amino-2-(2,6-difluoro-fenil)-N-(4-((1R,3S,5S)-3-hidroxi-5-metil-ciclohexil)-piridin-3-il)-tiazol-4-carboxamida, N-(4-((1R,3S,5S)-3-amino-5-metil-ciclohexil)-piridin-3-il)-2-(2,6-difluoro-fenil)-tiazol-4-carboxamida, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de las mismas.

13. Un método para el tratamiento de una condición mediante la modulación de la actividad de integración 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 cualquiera desde la reivindicación 1 hasta la reivindicación 12.

14. Una composición que comprende una cantidad terapéuticamente efectiva del compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12, o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, junto con un vehículo farmacéuticamente aceptable.

15. Un método para inhibir la actividad de la cinasa PIM en una célula, el cual comprende poner en contacto la célula con una cantidad efectiva de un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12.

15. Un método para el tratamiento de una condición mediante la modulación de la actividad de integración del provirus de la cinasa

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Maloney (cinasa PIM), el cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12.

16. Un método para inhibir la actividad de la cinasa PIM en un paciente, el cual comprende administrar al paciente una composición que comprende una cantidad farmacológicamente efectiva de un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12.

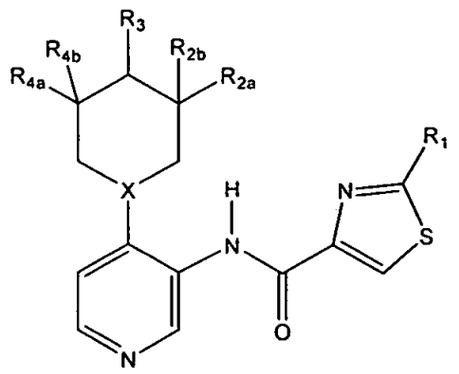
17. Un método para el tratamiento de un trastorno de cáncer en un paciente, el cual comprende administrar al paciente una composición que comprende una cantidad de un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12, efectiva para inhibir la actividad de la cinasa PIM en el paciente.

18. Un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12, para utilizarse como un agente terapéutico.

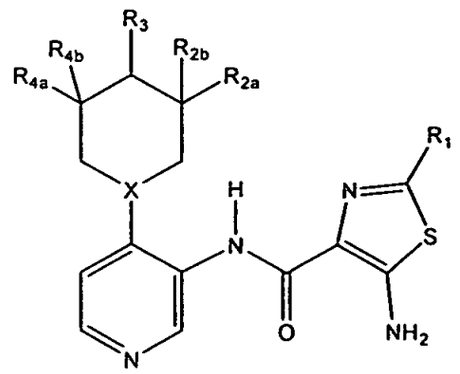
19. Un compuesto de cualquiera desde la reivindicación 1 hasta la reivindicación 12, para utilizarse en la fabricación de un medicamento para el tratamiento de cáncer.

RESUMEN

La presente invención se refiere a nuevos compuestos de las fórmulas I y II, a sus tautómeros, estereoisómeros y polimorfos, y a las sales farmacéuticamente aceptables, ésteres, metabolitos o profármacos 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 inhibición de la actividad de la cinasa Pim y/o en la profilaxis o el tratamiento de cáncer.



(I)



(II)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2009/052506	03.03.2009	03.03.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D417/12 C07D417/14 A61K31/4439 A61P35/00

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Brandstetter, T Telephone No. +49 89 2399-5847

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2009/052506

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

Reference is made to the following documents:

D1: CA-A1-2 649 043 (ASTELLAS PHARMA INC [JP]) 1 November 2007 (2007-11-01)

D2: WO 2007/058942 A (SCHERING CORP [US]; ZHAO LIANYUN [US]; CURRAN PATRICK J [US]; BELANGER) 24 May 2007 (2007-05-24)

2. Introductory remarks

The application lists two claims referred to as claim 15. The second thereof is an exact copy of claim 13 and is ignored in the following considerations. In other words, when referring to claim 15 the following considerations refer only to the subject-matter of the claim 15 first mentioned in the application.

Claims 13 and 15-17 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3. Novelty (Article 33(2) PCT)

The document D1 shows (the references in parentheses applying to this document) compounds of the general formula (I) (claim 1) which exhibit inhibitory activity on the trkA receptor (p. 66, line 4-6) and pharmaceutical compositions comprising them (claim 9). Formula (I) of D1 overlaps with formula(I) of the present application if the residues of formula (I) of D1 are chosen as follows: X is S, A is pyridinediyl, Q is monocyclic nitrogen-containing heterocyclic group, R^1 is lower cycloalkyl which may be substituted or aryl which may be substituted, and R^2 is H; and the residues of formula (I) of the

present application are chosen as follows: X = N.
However specific compounds falling into that overlap have not been disclosed in D1 and the compounds falling into that overlap can be regarded as a novel selection because the combination of substituents as defined above is narrow and reasonably different from the compounds disclosed in D1. The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

Compounds according to formula II of claim 2 have not been disclosed in the prior art and the subject-matter of claim 2 therefore complies with Article 33(2) PCT.

Claims 3-12 are dependent on claims 1 or 2 and as such also meet the requirements of the PCT with respect to novelty.

Claims 13-19 refer to the use of compounds according to claim 1 or 2 or compositions comprising them, and therefore also comply with Article 33(2) PCT.

4. Inventive step (Article 33(3) PCT)

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-19 involves an inventive step in the sense of Article 33(3) PCT.

4.1. The document D2 is regarded as being the closest prior art to the subject-matter of the present application, and discloses (the references in parentheses applying to this document): Compounds of formula I (claim 1) their use to inhibit PIM kinases (claim 59) and to treat cancer (claim 63).

4.2. The compounds according to claims 1 and 2 differ from these known PIM kinase inhibitors in their structure; they do not contain a imidazo[1,2-a]pyrazine core.

4.3. The problem to be solved by the present invention may be regarded as the provision of alternative PIM kinase inhibitors for the treatment of cancer. It has been solved by the provision of compounds of formula I and II which inhibit PIM kinases (cf. table p. 130-137).

4.4. The solution to this problem proposed in claims 1-12 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: Neither D2 nor any other prior art has suggested compounds of formula (I) of the present application as PIM kinase inhibitors nor has it been obvious for a person skilled in the art, that said compounds could be active as PIM kinase inhibitors.

Re Item VI

Reference is made to the following documents:

D3: WO 2008/054701 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08)
D4: WO 2008/054702 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08)
D5: WO 2008/054749 A (SCHERING CORP [US]; SHIPPS GERALD W JR [US]; CHENG CLIFF C [US]; HUANG) 8 May 2008 (2008-05-08)

Documents D3-D5 will become relevant in particular for inventive step if the claimed priority of the present application turns out not to be valid.

Re Item VIII
Reasoned statement with regard to clarity

The application does not meet the requirements of Article 6 PCT, because claims 2 and 13-17 are not clear.

For the terms "cycloalkyl", and "aryl" used in claim 2, definitions are found in the description (p. 11, lines 29-31 and p. 12 line 7-9) which do not follow the meaning and scope which they normally have in the art. Claim 2 should therefore be amended in such a way, that its meaning is clear from the wording of the claim alone.

Claim 13 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (by their capability of modulating PIM kinase), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).
The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.

Remarks:

The "second" claim 15, which is an exact copy of claim 13 (cf. above) is an obvious error and should be deleted.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Industria y Comercio
SUPERINTENDENCIA

No. 10-110544- -00000-0000

Fecha: 2010-09-07 16:13:15 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 205

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	10 110544
	Solicitud internacional	PCT/EP2009/052506
	Fecha inicio fase nacional	03/10/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14070

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 29 OCT. 2010.
adpa11